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HIV Medicine 2003

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Contributing Authors

Marcus Altfeld – Boston

Georg Behrens – Melbourne

Mario Ostrowski – Toronto

Andrea Rubbert – Köln

Christiane Schieferstein – Frankfurt

Reinhold E. Schmidt – Hannover

Bruce D. Walker – Boston

Eva Wolf – München

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Edited by

Christian Hoffmann

and

Bernd Sebastian Kamps

Flying Publisher

Editors

Christian Hoffmann, M.D.

University of Schleswig Holstein
Infectious Diseases Outpatient Clinic Kiel
Chemnitzstr. 33
24116 Kiel, Germany
Fax: + 49 431 1697 1273
www.HIVMedicine.com
www.SARSReference.com

Bernd Sebastian Kamps, M.D.

Flying Publisher
Rue Saulnier
75009 Paris
France
www.FlyingPublisher.com

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Preface

Hardly any field of medicine has ever undergone a similar stormy development to that of the therapy of HIV infection. Little more than 10 years passed, between the discovery of the pathogen and the first effective treatment! However, there is also hardly a field that is subjected to so many fast- and short-lived trends. What today seems to be statute, is tomorrow often already surpassed. Nevertheless, therapeutical freedom must not be confused with freedom of choice. This book presents the medical knowledge that is actual today: from December 2002 to January 2003.

Because HIV medicine changes so fast, HIV Medicine 2003 will be updated every year. Additional chapters about opportunistic infections, malignancies and hepatitis are freely available at our Web site www.HIVMedicine.com.

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Christian Hoffmann and Bernd Sebastian Kamps

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Contributing Authors

Marcus Altfeld, M.D.

Partners AIDS Research Center
Massachusetts General Hospital
Bldg. 149, 13th Street, 5th floor
Charlestown, MA 02129
USA

Tel: 617-724-2461

Fax: 617-726-5411

MAltfeld@partners.org

Georg Behrens, M.D.

Immunology Division
Walter And Eliza Hall Institute of Medical Research
PO Royal Melbourne Hospital
Parkville, 3050, Victoria
Australia

Fax: 61-3-9347-0852

behrens@wehi.edu.au

Mario Ostrowski, M.D.

Clinical Sciences Division
University of Toronto
Medical Sciences Building, Rm 6271
1 King's College Circle
Toronto, ON M5S 1A8
Canada

Tel: 416-946-5805

FAX: 416-978-8765

E-mail: m.ostrowski@utoronto.ca

6 Contributing Authors

Andrea Rubbert, M.D.

Medizinische Klinik I
Universitätsklinik Köln
Joseph-Stelzmann Str 9
50924 Köln
Germany
Tel +49 221-478-5623
Fax: +49 221-478-6459

Christiane Schieferstein, M.D.

Medizinische Klinik II
Uniklinikum Frankfurt
Theodor-Stern-Kai 7
60590 Frankfurt am Main
Germany
Tel: +49 69-6301-0
schieferstein@wildmail.com

Reinhold E. Schmidt, M.D., Ph.D.

Abteilung Klinische Immunologie
Zentrum Innere Medizin der
Medizinischen Hochschule Hannover
Carl-Neuberg-Straße 1
30625 Hannover
Germany
Tel: +49 511-532-6656
Fax: +49 511-532-9067
Schmidt.Reinhold.Ernst@MH-Hannover.de

Bruce D. Walker, M.D., Ph.D.

Partners AIDS Research Center
Massachusetts General Hospital
Bldg. 149, 13th Street, 5th floor
Charlestown, MA 02129
USA

Tel: 001 617-724-8332

Fax: 001 617-726-4691

bwalker@helix.mgh.harvard.edu

Eva Wolf, Dipl. Phys. Univ., M.P.H.

MUC Research GmbH
Karlsplatz 8
80335 München
Germany

Tel: +49 89 - 558 70 30

Fax: +49 89 - 550 39 41

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Chapter 1:

Pathogenesis of HIV-1 Infection

Andrea Rubbert and Mario Ostrowski

Introduction

Since the initial description of the human immunodeficiency virus type I (HIV-1) in 1983 (1,2) and HIV-2 in 1986 (3), these two viruses have been identified for almost 20 years as the primary cause of the acquired immunodeficiency syndrome (AIDS). As HIV-1 is the major cause of AIDS in the world today, our discussion will be primarily limited to HIV-1 infection. Worldwide, the number of HIV-1 infected persons exceeds 40 million, the majority of whom live in the developing countries of Asia, sub-Saharan Africa and South America.

The introduction of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI) to antiretroviral treatment regimens in 1995 began the era of highly active antiretroviral therapy (HAART), and resulted in dramatic improvements in the mortality and morbidity of HIV disease, as determined by a decreased incidence of opportunistic infections, tumors, and deaths. Despite all the therapeutic advantages achieved during the last decade, including the development of highly active antiretroviral therapy ("HAART"), once an individual has become infected, eradication of the virus still remains impossible. In addition, new problems relating to the short- and long-term toxicity of drug treatments and the occurrence of resistance mutations in both circulating and transmitted viruses are emerging. In most countries in South East Asia and Africa, the incidence and prevalence of HIV-1 infection continues to increase and surpass that of Europe and North America. However, due to the high costs of drug regimens and the lack of a healthcare infrastructure in these developing countries, the

widespread use of HAART is currently not feasible. The further course of the HIV-1 pandemic therefore mainly depends on how and to what degree the developing countries with a high HIV-1 prevalence are able to take advantage of the medical progress achieved in Europe and North America, and whether an effective prophylactic vaccine might become available in the near future.

An understanding of the immunopathogenesis of HIV-1 infection is a major *prerequisite* for rationally improving therapeutic strategies, developing immunotherapeutics and prophylactic vaccines. As in other virus infections, the individual course of HIV-1 infection depends on both host and viral factors.

The course of infection with HIV-1 in HIV-infected humans may vary dramatically, even though the primary infections arose from the same source (4). In some individuals with a long-term nonprogressive HIV-1 infection (i.e. lack of decline in CD4 counts, or chronic infection for at least seven years without the development of AIDS), a defective virion was identified (5). Thus, infection with a defective virus, or one which has a poor capacity to replicate, may prolong the clinical course of HIV-1 infection. However, in most individuals HIV-1 infection is characterized by a replication competent virus with a high turn-over of virions produced daily. Host factors may also determine whether or not an HIV-1 infected individual will rapidly develop clinically overt immunodeficiency or whether this individual may belong to the group of long-term nonprogressors, who represent about 5% of all infected patients. The identification and characterization of host factors contributing to the course of HIV infection, including immunological defense mechanisms and genetic factors, will be crucial for our understanding of the immunopathogenesis of HIV infection and for the development of immunotherapeutic and prophylactic strategies.

The Structure of HIV-1

HIV-1 is a retrovirus and belongs to the family of lentiviruses. Infections with lentiviruses typically show a chronic course of disease, a long period of clinical latency, persistent viral replication and involvement of the central nervous system. Visna infections in sheep, simian immunodeficiency virus infections (SIV) in monkeys, or feline immunodeficiency virus infections (FIV) in cats are typical examples of lentivirus infections.

Using electron microscopy, HIV-1 and HIV-2 resemble each other strikingly. However, they differ with regard to the molecular weight of their proteins, as well as having differences in their accessory genes. HIV-2 is genetically more closely related to the SIV found in sootey mangabeys (SIVsm) rather than HIV-1 and it is likely that it was introduced into the human population by monkeys. Both HIV-1 and HIV-2 replicate in CD4⁺ T cells and are regarded as pathogenic in infected persons although the actual immune deficiency may be less severe in HIV-2 infected individuals.

The Morphologic Structure of HIV-1

HIV-1 viral particles have a diameter of 100 nm and are surrounded by a lipoprotein membrane. Each viral particle contains 72 glycoprotein complexes which are integrated into this lipid membrane and are each composed of trimers of an external glycoprotein gp120 and a transmembrane spanning protein gp41. The bonding between gp120 and gp41 is only loose and therefore gp120 may be shed spontaneously within the local environment. Glycoprotein gp120 may also be detected in the serum (6) as well as within the lymphatic tissue of HIV-infected patients (7). During the process of budding, the virus may also incorporate, from the membrane of the host cell into its lipoprotein layer, different host proteins, such as HLA class I and II proteins, or adhesion proteins, such as ICAM-1 that may facilitate adhesion to other target cells. The matrix protein p17 is anchored to the inside of the viral lipoprotein membrane. The p24

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core antigen contains two copies of HIV-1 RNA. The HIV-1 RNA is part of a protein-nucleic acid complex, which is composed of the nucleoprotein p7 and the reverse transcriptase p66 (RT). The viral particle contains all the enzymatic equipment that is necessary for replication: a reverse transcriptase (RT), an integrase p32 and a protease p11 (overview in: 8) (Fig. 1).

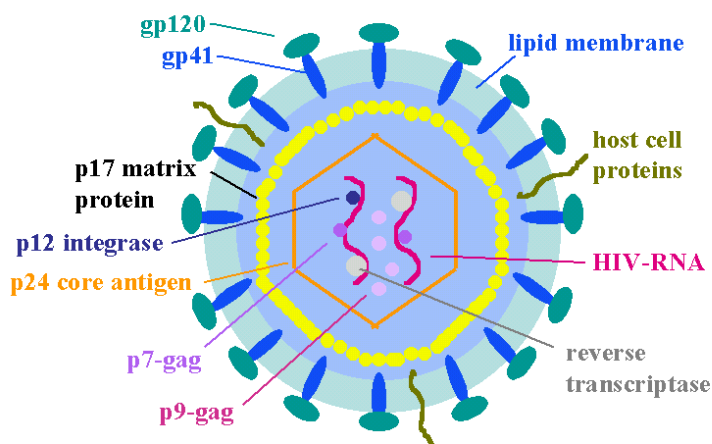


Figure 1: Structure of a HIV virion particle. For detailed explanations see text.

The Organization of the Viral Genome

Most replication competent retroviruses depend on three genes: *gag*, *pol* and *env* : **gag** means "group-antigen", **pol** represents "polymerase" and **env** is for "envelope" (overview in: 9) (Fig. 2). The "classical" structural scheme of a retroviral genome is: 5'LTR-gag-pol-env-LTR 3'. The LTR ("long terminal

repeat") regions represent the two end parts of the viral genome that are connected to the cellular DNA of the host cell after integration and do not encode for any viral proteins. The *gag* and *env* genes code for the nucleocapsid and the glycoproteins of the viral membrane; the *pol* gene codes for the reverse transcriptase and other enzymes. In addition, HIV-1 contains in its 9kB RNA six genes (*vif*, *vpu*, *vpr*, *tat*, *rev* and *nef*) that contribute to its genetic complexity. *Nef*, *vif*, *vpr* and *vpu* were classified as accessory genes in the past, as they are not absolutely required for replication in vitro. However, the regulation and function of these accessory genes and their proteins have been studied and characterized in more detail within the last years. The accessory genes, *nef*, *tat* and *rev*, are all produced early in the viral replication cycle.

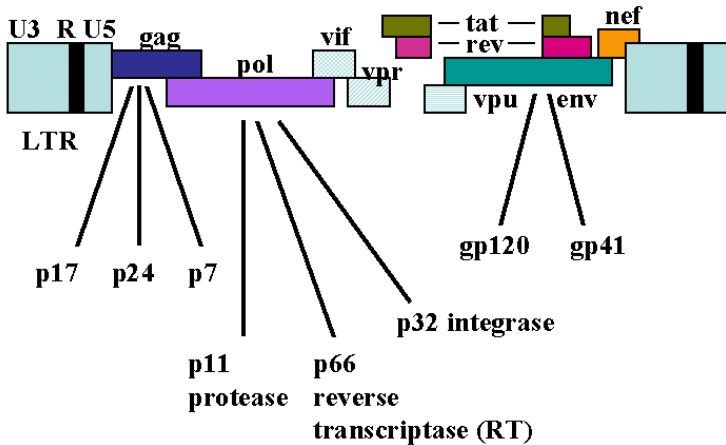


Figure 2: HIV and its genes. For detailed explanations see text.

Tat and *rev* are regulatory proteins that accumulate within the nucleus and bind to defined regions of the viral RNA: TAR

(transactivation-response elements), found in the LTR; and RRE (rev response elements), found in the *env* gene, respectively. The *tat* protein is a potent transcriptional activator of the LTR promoter region and is essential for viral replication in almost all in vitro culture systems. Cyclin T1 is a necessary cellular cofactor for *tat* (10). *Tat* and *rev* stimulate the transcription of proviral HIV-1-DNA into RNA, promote RNA elongation, enhance the transportation of HIV-RNA from the nucleus to the cytoplasm and are essential for translation. *Rev* is also a nuclear export factor that is important for switching from the early expression of regulatory proteins to the structural proteins that are synthesized later.

Nef has been shown to have a number of functions. *Nef* may induce downregulation of CD4 (11) and HLA class I and II molecules (12) from the surface of HIV-1 infected cells, which may represent an important escape mechanism for the virus to evade an attack mediated by cytotoxic CD8⁺ T cells and to avoid recognition by CD4⁺ T cells. *Nef* may also interfere with T cell activation by binding to various proteins that are involved in intracellular signal transduction pathways (overview in:13).

In SIV-infected rhesus macaques, an intact *nef* gene was essential for a high rate of virus production and the progression of disease. HIV-1 with deletions in *nef* was identified in a cohort of Australian long-term non-progressors (5). However, more recent reports indicate that some of these patients are now developing signs of disease progression together with a decline of CD4⁺ T cells. Thus, although deletions of the *nef* gene may slow viral replication, they cannot always prevent the development of AIDS.

Vpr seems to be essential for viral replication in non-dividing cells such as macrophages. *Vpr* may stimulate the HIV-LTR in addition to a variety of cellular and viral promoters. More recently, *vpr* was shown to be important for the transport of the viral preintegration complex to the nucleus (overview in: 14) and may arrest cells in the G2 phase of the cell cycle.

Vpu is important for the virus "budding" process, because mutations in *vpu* are associated with persistence of the viral particles at the host cell surface. *Vpu* is also involved when CD4-gp160 complexes are degraded within the endoplasmatic reticulum and therefore allows recycling of gp160 for the formation of new virions (15).

Vif is important for intracellular transport mechanisms of viral components. Co-localization of *vif* with vimentin, a protein belonging to the cellular cytoskeleton, was demonstrated. Virions that are deficient in *vif* may still be transmitted from cell to cell, but not from a cell free medium. *Vif* also seems to affect viral morphogenesis (Overview in: 16).

The HIV Replication Cycle

HIV Entry

CD4 as a primary receptor for HIV

CD4 is a 58 kDa monomeric glycoprotein that can be detected on the cell surface of about 60% of T-lymphocytes, of T-cell precursors within the bone marrow and thymus, and on monocytes and macrophages, eosinophils, dendritic cells and microglia cells of the central nervous system. The extracellular domain of CD4 on T cells is composed of 370 amino acids; the hydrophobic transmembrane domain and the cytoplasmic part of CD4 on T cells consist of 25 and 38 amino acids, respectively. Within the extracellular part of CD4, four regions D1-D4 have been characterized that represent immunoglobulin-like domains. Residues within the V2 region of CD4 (amino acids 40-55) are important for the binding of gp120 to CD4 and this region overlaps the part of the CD4 where its natural ligands, HLA class II molecules, bind.

The identification of the gp120 binding site on the CD4 of CD4⁺ T cells stimulated attempts to use soluble CD4 (sCD4) to neutralize the circulating virus in patients, with the goal being

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the inhibition of viral spread. However it became evident that even though laboratory viral isolates were easily neutralized by sCD4, a neutralization of primary, patient-derived isolates had not been achieved.

In contrast, sCD4 was able to induce conformational changes within the viral envelope that promoted the infection of target cells (18).

CD4 attaches to the T cell receptor complex (TCR) on CD4⁺ T cells and binds to the HLA class II molecules on antigen-presenting cells. The binding of gp120 to CD4 is not only a crucial step for viral entry, but also interferes with intracellular signal transduction pathways and promotes apoptosis in CD4⁺ T cells (19).

CD4, as a primary and necessary receptor for HIV-1, HIV-2 and SIV, was already characterized in 1984 (20, 21). However, experiments using non-human cell lines transfected with human CD4 showed that expression of human CD4 on the cell surface of a non-human cell line was not sufficient to allow entry of HIV. Therefore the existence of additional human co-receptors necessary for viral entry was postulated. On the other hand, some laboratory HIV-1 isolates as well as some HIV-2 and SIV isolates are able to infect human cells independently from CD4. Interestingly, monoclonal antibodies against CD4 induced conformational (CD4I) epitopes to bind to the gp120 of CD4-independent viruses. This observation suggests that the gp120 of CD4-independent viruses already exposes the regions that are necessary for co-receptor recognition and binding and therefore binding to CD4 is not a *prerequisite* of entry for these viruses. CD4-independent viruses are easy to neutralize using the serum of HIV-infected patients, suggesting that the immune response selects against CD4-independent viruses (22).

Chemokine receptors as co-receptors for HIV entry

A milestone for the characterization of the early events leading to HIV-1 entry was an observation by Cocchi and his co-workers in 1995. CD8⁺ T cells from HIV-infected patients are

able to suppress viral replication in co-cultures with HIV-infected autologous or allogenic CD4⁺ T cells and this is independent from their cytotoxic activity (23). Cocchi identified the chemokines MIP-1 α , MIP-1 β and Rantes in supernatants from CD8⁺ T cells derived from HIV-infected patients, and was able to show that these chemokines were able to suppress replication in a dose-dependent manner of some, but not all viral isolates tested (24). MIP-1 α , MIP-1 β and Rantes are ligands for the chemokine receptor CCR5, and a few months later several groups were able to show that CCR5 is a necessary co-receptor for monocyctotropic (M-tropic) HIV-1 isolates (25, 26, 27). A few weeks earlier, the chemokine receptor CXCR4 (fusin) was described as being the co-receptor used by T-cell tropic (T-tropic) HIV-isolates (28). Monocyctotropic (M-tropic) HIV-1 isolates are classically those viruses that are most easily propagated in macrophage cultures, are unable to infect T-cell lines (i.e., immortalized T cells), but are able to easily infect primary T cells from peripheral blood samples. Conversely, T-cell tropic HIV-1 isolates have classically been identified as being those that are easily propagated in T-cell lines, and grow poorly in macrophages, but are also able to easily infect primary T cells from peripheral blood samples. Thus, it should be noted that both M-tropic and T-tropic HIV-1 variants can easily infect primary human non-immortalized T cells in-vitro. Chemokines ("**Chemotactic cytokines**") and their receptors have been previously characterized with regard to their role in promoting the migration ("chemotaxis") of leukocytes and their proinflammatory activity.

Chemokines are proteins of 68-120 amino acids which depend on the structure of their common cysteine motif, and which may be subdivided into C-X-C (α -chemokines), C-C (β -chemokines) and C-chemokines. Chemokines typically show a high degree of structural homology to each other and may share the receptors they bind to. Chemokine receptors belong to the group of receptors with seven transmembranic regions ("7-

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transmembrane receptors"), which are intracellularly linked to G-proteins.

SDF-1 ("stromal cell-derived factor 1") was identified as the natural ligand of CXCR4 and is able to inhibit the entry of T-tropic HIV-1 isolates into activated CD4⁺ T cells. Rantes ("regulated upon activation T cell expressed and secreted"), MIP-1 α ("macrophage inhibitory protein") and MIP-1 β represent the natural ligands of CCR5 and are able to inhibit the entry of M-tropic HIV-1 isolates into T cells. A schematic model is depicted in Figure 3: T-tropic HIV-1 isolates mainly infect activated peripheral blood CD4⁺ T cells and cell lines and use CXCR4 for entry into the CD4⁺-positive target cell. M-tropic isolates are able to infect CD4⁺ T cells, monocytes and macrophages and depend on the use of CCR5 and CD4 for viral entry.

The interaction of gp120 and the cellular receptors is now understood in more detail. Gp120 primarily binds to certain epitopes of CD4. Binding to CD4 induces conformational changes in gp120 that promote a more efficient interaction of the V3 loop of gp120 with its respective co-receptor. Membrane fusion is dependent on gp120-co-receptor binding. Gp41, as the transmembrane part of the envelope glycoprotein gp160, is crucial for the fusion of the viral and the host cell membrane. Similar to influenza hemagglutinin, it was postulated that after binding of gp120 to CD4, a conformational change is also induced in gp41 that allows gp41 to insert its hydrophobic NH₂-terminal into the target cell membrane. Gp41 has been compared to a "mouse trap" and a crystallographic analysis of the ectodomainic structure of gp41 seems to confirm that hypothesis (29). The identification of crucial amino acid sequences for this process was used to synthesize peptides that may bind to gp41 within the domains that are critical for the induction of conformational changes and that may inhibit membrane fusion.

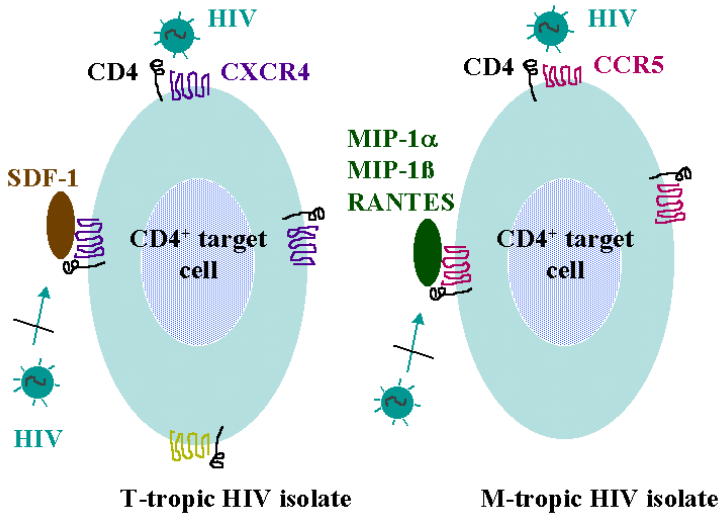


Fig 3: Inhibition of virus entry of CCR5-utilizing (monocytotropic) and CXCR4-utilizing (T-cell tropic) HIV isolates by the natural ligands of the chemokine co-receptors CCR5 and CXCR4.

T20 is the first of several peptides that bind to gp41 and has been tested in clinical trials for suppressing viral replication (30). Currently, T20 is available as a therapeutic option for selected patients. One disadvantage of T20 is that it must be taken intramuscularly rather than as a pill.

Using transfected cell lines, besides CCR5 and CXCR4, other chemokine receptors, such as CCR3, CCR2, CCR8, CCR9, STRL33 ("Bonzo"), Gpr 15 ("Bob"), Gpr 1, APJ and ChemR23, were identified and shown to be used for entry by certain HIV isolates (31, 32). APJ may represent a relevant co-receptor within the central nervous system. Despite this broad spectrum of potentially available co-receptors, CCR5 and CXCR4 seem to represent the most relevant co-receptors for HIV-1 in vivo.

The importance of CCR5 as the predominant co-receptor for M-tropic HIV isolates is underscored by another observation. The majority of individuals with a genetic defect of CCR5 are resistant to infection with HIV-1 (33). In vitro experiments show that lymphocytes derived from these individuals are resistant to HIV-1 infection using M-tropic isolates but not to infection with T-tropic isolates. Lymphocytes from these individuals do not express CCR5 on their cell surface and genetically they have a 32 base pair deletion of the CCR5 gene. Worldwide, a few patients have been identified that have acquired HIV-1 infection despite a homozygous deletion of the CCR5. As expected, all of them were infected with CXCR4-using HIV-1 isolates (34). In epidemiologic studies, the allelic frequency of the CCR5 gene deletion is 10-20% among Caucasians, particularly amongst those of Northern European descent. The frequency of a homozygous individual is about 1% in Caucasians (35). Studies conducted on African or Asian populations, however, do not find this 32 basepair deletion of the CCR5, suggesting that this mutation arose after the separation of these races in evolutionary history.

Individuals that are heterozygous for the 32 bp deletion of the CCR5 show a decreased expression of CCR5 on the cell surface and are more frequently encountered within cohorts of long-term non-progressors compared to patients who have a rapid progression of disease (35).

In addition to the 32bp deletion of the CCR5, other genetic polymorphisms, with regard to the chemokine receptors (CCR2) or their promoters (CCR5), were described. Based on the occurrence of these polymorphisms within defined patient cohorts, they were associated with a more rapid or a more favorable course of disease, depending on the particular polymorphism (36, 37).

In patients who have a rapid progression of disease (rapid drop in CD4⁺ T cell count), virus isolates that use CXCR4 as a predominant co-receptor tend to be frequently isolated from their cells, in comparison to patients with a stable CD4⁺ T cell count.

The expression of co-receptors on CD4⁺ lymphocytes depends on their activation level.

CXCR4 is mainly expressed on naive T cells, whereas CCR5 is present on activated and effector/memory T cells. During the early course of HIV-1 infection, predominantly M-tropic HIV-1 isolates are detected. Interestingly, M-tropic HIV-1 isolates are preferentially transmitted regardless of whether or not the "donor" predominantly harbors T-tropic isolates. At present, it remains unclear whether this "in vivo" preference of M-tropic HIV-1 isolates is determined by selected transportation of M-tropic isolates by submucosally located dendritic cells or whether the local cytokine/chemokine milieu favors the replication of M-tropic viruses. Recent intriguing studies by Cheng Meyer et al. suggest that M-tropic HIV-1 viruses are more easily able to 'hide' from the immune system by replicating in macrophages, in comparison to T-tropic viruses, thus giving them a survival advantage in the infected individual.

The blockade of CCR5 therefore seems to represent a promising target for therapeutic intervention. In vitro, monoclonal antibodies to CCR5 (2D7 and others) are able to block the entry of CCR5-using HIV isolates into CD4⁺ T cells and macrophages. Small molecule inhibitors of CCR5 have been designed and are currently being tested in clinical trials. In vitro studies, as well as experiments using SCID mice, however, suggest that blockade of CCR5-using isolates may alter their tropism towards increased usage of CXCR4.

Small molecule inhibitors like T22, ALX40-4C or AMD3100 are able to inhibit CXCR4 (59, 60) and are also subject to pre-clinical and clinical trials. Although the therapeutic use of chemokine receptor blockers seems promising, a lot of questions still remain unanswered. Chemokine analogs such as AOP-Rantes do not only inhibit, but also show agonistic activity and may not bind to CCR5 exclusively. Using knockout mice it was demonstrated that the absence of CXCR4 or SDF-1 is associated with severe defects in hematopoiesis and in cerebellar development (61). Currently, it remains unclear whether

the blockade of CXCR4 in postnatal or adult individuals may also affect other organ systems.

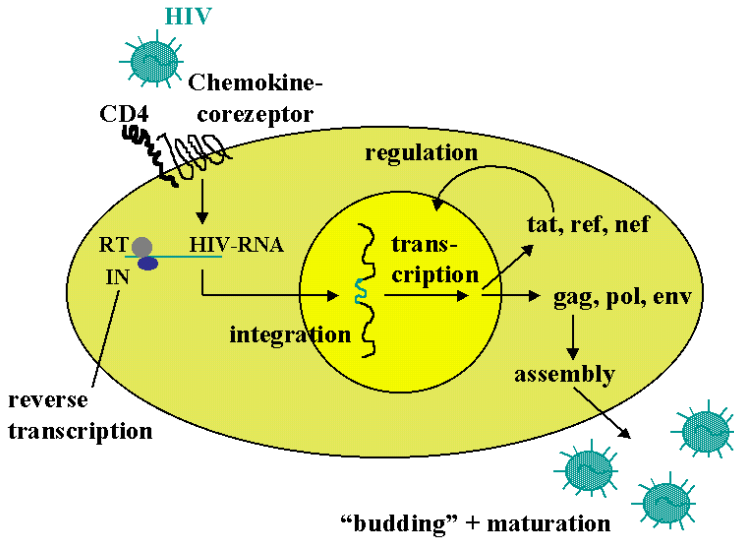


Fig 4: HIV life cycle within a CD4⁺ T cell.

Postfusion Events

HIV-1 entry into quiescent T cells is comparable to HIV-1 entry into activated T cells, but synthesis of HIV-1 DNA remains incomplete in quiescent cells (38). The conversion of viral RNA into proviral DNA, mediated by the viral enzyme reverse transcriptase (RT), occurs in the cytoplasm of the target cell and is a crucial step within the viral replication cycle (see Fig. 4). Blockade of the RT by the nucleoside inhibitor, zidovudine, was the first attempt to inhibit viral replication in HIV-1 infected patients. To-day, numerous nucleoside, nucleotide and non-nucleoside RT inhibitors are available for clinical use and

have broadened the therapeutic arsenal substantially since the mid-eighties.

Reverse transcription occurs in multiple steps. After binding of the tRNA primers, synthesis of proviral DNA occurs as a minus-strand polymerization starting at the PBS ("primer binding site") up to the 5' repeat region as a short R/U5 DNA. The next step includes degradation of RNA above the PBS by the viral enzyme RNAase H and a "template switch" of the R/U5 DNA with hybridization at the R sequence at the 3' RNA end. Now the full length polymerization of proviral DNA with degradation of the tRNA is completed. Reverse transcription results in double-stranded HIV DNA with LTR regions ("long terminal repeats") at each end.

HIV-1 enters into quiescent T cells and reverse transcription may result in the accumulation of proviral, non-integrating HIV-DNA. However, cellular activation is necessary for integration of the proviral HIV DNA into the host cell genome after transportation of the pre-integration complex into the nucleus (38). Cellular activation may occur in vitro after stimulation with antigens or mitogens, in vivo activation of the immune system is observed after antigen contact or vaccination or during an opportunistic infection. In addition, evidence is emerging that HIV-1 gp120 itself may activate the infecting cell to enhance integration. Besides monocytes, macrophages and microglial cells, latently infected quiescent CD4⁺ T-cells that contain non-integrated proviral HIV-DNA represent important long-living cellular reservoirs for HIV (39). Since natural HIV-1 infection is characterized by continuing cycles of viral replication in activated CD4⁺ T-cells, viral latency in these resting CD4⁺ T-cells likely represents an accidental phenomenon and is not likely to be important in the pathogenesis of this disease. This small reservoir of latent provirus in quiescent CD4⁺ T-cells gains importance, however, in individuals who are treated with HAART, since the antivirals are unable to affect non-replicating proviruses and thus the virus will persist in those cells and be replication competent to supply new rounds of infection, if the

drugs are stopped. Thus, the existence of this latent reservoir has prevented HAART from entirely eradicating the virus from infected individuals.

Cellular transcription factors like NF- κ B may also bind to the LTR regions. After stimulation with mitogens or cytokines, NF- κ B is translocated into the nucleus where it binds to the HIV-LTR region, thereby initiating transcription of HIV genes. Transcription initially results in the early synthesis of regulatory HIV-1 proteins such as *tat* or *rev*. *Tat* binds to the TAR site ("transactivation response element") at the beginning of the HIV-1 RNA in the nucleus and stimulates transcription and the formation of longer RNA transcripts. *Rev* activates the expression of structural and enzymatic genes and inhibits the production of regulatory proteins, therefore promoting the formation of mature viral particles. The proteins coded for by *pol* and *gag* form the nucleus of the maturing HIV particle; the gene products coded for by *env* form the gp120 "spikes" of the viral envelope. The gp120 spikes of the envelope are synthesized as large gp160-precursor molecules and are cleaved by the HIV-1 protease into gp120 and gp41. The *gag* proteins are also derived from a large 53 kD precursor molecule, from which the HIV-protease cleaves the p24, p17, p9 and p7 *gag* proteins. Cleavage of the precursor molecules by the HIV-1 protease is necessary for the generation of infectious viral particles, and therefore the viral protease represents another interesting target for therapeutic blockade (40). The formation of new viral particles is a stepwise process: a new virus core is formed by HIV-1 RNA, *gag* proteins and various *pol* enzymes and moves towards the cell surface. The large precursor molecules are cleaved by the HIV-1 protease, which results in the infectious viral particles budding through the host cell membrane. During the budding process, the virus lipid membranes may incorporate various host cell proteins and become enriched with certain phospholipids and cholesterol. In contrast to T cells, where budding occurs at the cell surface and virions are released into the extracellular space, the budding process in monocytes and macro-

phages results in the accumulation of virions within cellular vacuoles.

The replication of retroviruses is error prone and is characterized by a high spontaneous mutation rate. On average, re-verse transcription results in 1-10 errors per genome and per round of replication. Mutations can lead to the formation of replication-incompetent viral species, but mutations causing drug resistance may also accumulate, which, provided that there is selection pressure under certain antiretroviral drugs and incomplete suppression of viral replication, may be outgrowing.

In addition, viral replication is dynamic and turns over quickly in infected individuals at an average rate of 10^9 new virus particles being produced and subsequently cleared per day. Thus, within any individual, because of the extensive virus replication and mutation rates, there exists an accumulation of many closely related virus variants within the 'population' of viruses, referred to as a viral "quasispecies". The selection pressure on mostly the pre-existing mutations may not only be exerted by certain drugs, but also by components of the immune system, such as neutralizing antibodies or cytotoxic T cells (CTL).

HIV and the Immune System

The Role of Antigen-Presenting Cells in the Pathogenesis of HIV Infection

Dendritic cells as prototypes of antigen-presenting cells

Dendritic cells, macrophages and B cells represent the main antigen-presenting cells of the immune system. Dendritic cells (DC) are the most potent inducers of specific immune responses and are considered essential for the initiation of primary antigen-specific immune reactions. DC precursors migrate from the bone marrow towards the primary lymphatic organs and into the submucosal tissue of the gut, the genitourinary and the respiratory tracts. They are able to pick up and process soluble anti-

gens and migrate to the secondary lymphatic organs, where they activate antigen-specific T cells.

DC represent a heterogeneous family of cells with different functional capacities and expression of phenotypic markers, depending on the local microenvironment and the stage of maturation. Immature DC have the capacity to pick up and process foreign antigens, but do not have great T cell stimulatory capacities. However, mature DC show a predominant immunostimulatory ability. DC in tissues and Langerhans cells, which are specialized DC in the skin and mucosal areas, represent a more immature phenotype and may take up antigen. Once these DC have taken up the antigen they migrate to the lymphoid tissues where they develop a mature phenotype.

The stimulation of CD8⁺ T lymphocytes and the formation of antigen-specific cytotoxic T-cells (CTL) depend on the presentation of a peptide together with MHC class I antigens. DC may become infected with viruses, for instance influenza. Viral proteins are then produced within the cytoplasm of the cell, similar to cellular proteins, then degraded to viral peptides and translocated from the cytosol into the endoplasmic reticulum, where they are bound to MHC class I antigens. These peptide-MHC class I complexes migrate to the DC surface. The number of specific antigen-MHC class I complexes is usually limited and must eventually be recognized by rare T cell clones, up to a ratio of 1:100.000 or less. The T-cell receptor (TCR) may display only a low binding affinity (1 mM or less). The high density of co-stimulatory molecules on the DC surface, however, enhances the TCR-MHC:peptide interaction allowing efficient signaling to occur through the T cell and resulting in proliferation (clonal expansion) of the T cell. Virus-infected cells or tumor cells often do not express co-stimulatory molecules, and thus may not be able to induce a clonal expansion of effector cells. This underscores the importance of having a highly specialized system of antigen-presenting cells, i.e. DC, in operation to prime T cells to expand and proliferate initially.

The interaction of dendritic cells and B/T-cells

B- and T-lymphocytes may be regarded as the principle effector cells of antigen-specific immune responses. However, their function is under the control of dendritic cells. DC are able to pick up antigens in the periphery. These antigens are processed and expressed on the cell surface, together with co-stimulatory molecules that initiate T cell activation. B cells may recognize antigen after binding to the B cell receptor. Recognition of antigen by T cells requires previous processing and presentation of antigenic peptides by DC. T cells express different T cell receptors (TCR), that may bind to the peptide:MHC class I on the surface of dendritic cells to allow activation of CD8⁺ T cells, or to the peptide:MHC class II molecules, to activate CD4⁺ T cells. The ability of DC to activate T cells also depends on the secretion of stimulatory cytokines such as IL-12, which is a key cytokine for the generation and activation of T_H1 and natural killer (NK-) cells.

Only a few DC and small amounts of antigen are sufficient to induce a potent antigen-specific T cell response, thus demonstrating the immunostimulatory potency of DC. The expression of adhesion molecules and lectins, such as DC-SIGN, support the aggregation of DC and T cells and promote the engagement of the T cell receptor (TCR). DC-SIGN is a type C lectin that has also been shown to bind to lentiviruses such as SIV and HIV-1 and -2 by interaction of gp120 with carbohydrates. In vivo, immunohistochemical studies show expression of DC-SIGN on submucosal and intradermal DC, suggesting an implication of DC-SIGN in vertical and mucosal transmission of HIV. The expression of DC-SIGN was shown to enhance the transmission of HIV to T cells and allows utilization of co-receptors if their expression is limited. Thus DC-SIGN may be a mechanism whereby HIV-1 is taken up by DC in the mucosal tissues. It is then transported by the DC to the lymphoid tissues, where HIV-1 can then infect all the residing CD4⁺ T cells.

Lymphatic Tissue as the Site of Viral Replication

Viral replication within the lymphatic tissue is already extensive in the early stages of the disease (42,43). During the initial phase of HIV-1 infection, there is a burst of virus into the plasma, followed by a relative decline in viremia. During this time, a strong HIV-1 specific cytotoxic T cell response is generated, which coincides with the early suppression of plasma viremia in most patients. Virions are trapped by the follicular dendritic cell (FDC) network within the lymphoid tissue. Macrophages, and activated and quiescent CD4⁺ T cells are the main targets of infection. During the whole course of infection with HIV-1, the lymphoid tissue represents the principle site of HIV-1 replication. The frequency of cells containing proviral DNA is 5-10x higher in lymphoid tissue than in circulating peripheral mononuclear cells in the blood, and the difference in viral replication in lymphoid tissue exceeds that in the peripheral blood by about 10-100x. Thus, the virus mainly accumulates in the lymph nodes.

After entry of HIV-1 into a quiescent CD4⁺ T cell and after completion of reverse transcription, the viral genome is represented by proviral unintegrated HIV DNA. The activation of CD4⁺ T cells is necessary for the integration of the HIV DNA into the host cell genome and is therefore a prerequisite for the synthesis of new virions. In this regard, the micromilieu of the lymphoid tissue represents the optimal environment for viral replication. The close cell-cell contact between CD4⁺ T-cells and antigen-presenting cells, the presence of infectious virions on the surface of the FDC, and an abundant production of pro-inflammatory cytokines such as IL-1, IL-6 or TNF α , promotes the induction of viral replication in infected cells and augments viral replication in cells already producing the virus. It should be noted that both IL-1 and TNF α induce NF-kb which binds to the HIV-1 LTR to promote proviral transcription. The importance of an antigen-induced activation of CD4⁺ T cells is underlined by several in vivo and in vitro studies that demonstrate

an increase of HIV-1 replication in association with a tetanus or influenza vaccination or an infection with *Mycobacterium tuberculosis* (44). Even though the clinical benefit of vaccination against common pathogens (e.g. influenza and tetanus) in HIV-1 infected patients outweighs the potential risk of a temporary increase in viral load, these studies indicate that in every situation where the immune system is activated, enhanced viral replication can also occur.

Patients undergoing HAART demonstrate a dramatic decrease in the number of productively infected $CD4^+$ T cells within the lymphoid tissue (45). However, in all patients examined so far, there persists a pool of latently infected quiescent T cells despite successful suppression of plasma viremia (39). It is these latently infected cells which may give rise to further rounds of viral replication, if the antiviral drugs are stopped.

During the natural course of HIV-1 disease, the number of $CD4^+$ T cells slowly decreases while plasma viremia rises in most patients. If sequential analysis of the lymphoid tissue is performed, progression of the disease is reflected by destruction of the lymphoid tissue architecture and a decreased viral trapping. Various immunohistological studies indicate that the paracortex of the lymph nodes represents the primary site where HIV replication is initiated (42,43). Infection of the surrounding $CD4^+$ T cells, as well as the initiation of T cell activation by DC, contributes to the spreading of HIV-1 within the lymphoid environment.

The HLA System and the Immune Response against HIV

$CD8^+$ T cells recognize "their" antigen (peptide) in context with HLA class I molecules on antigen-presenting cells, whereas $CD4^+$ T cells require the presentation of antigenic peptides in context with HLA class II molecules. The generation of an HIV specific immune response is therefore dependent on the individual HLA pattern.

Antigen-presenting cells may bind HIV peptides in different ways within "grooves" on the HLA class I molecules. Therefore, CD8⁺ T cells can be activated in an optimal or suboptimal way or may not be activated at all. Using large cohorts of HIV-1 infected patients, in whom the natural course of disease (fast versus slow progression) is known, HLA patterns were identified that were associated with a slow versus fast disease progression. These studies suggest that the HLA type could be responsible for the benign course of disease in about 40% of patients with a long-term non-progressive course of disease. Homozygosity for HLA Bw4 is regarded as being protective. Patients who display heterozygosity at the HLA class I loci are characterized by a slower progression of immunodeficiency than patients with homozygosity at these loci (46).

An initial study by Kaslow in 1996 demonstrated that HLA B14, B27, B51, B57 and C8 are associated with a slow disease progression; in contrast, the presence of HLA A23, B37 and B49 were associated with the rapid development of immunodeficiency (47).

All patients with HLA B35 had developed symptoms of AIDS after 8 years of infection.

More recent studies suggest that discordant couples with a "mismatch" at the HLA class I have a protective effect towards heterosexual transmission (48).

In vitro studies in HLA B57 positive patients demonstrate that these patients display HLA B57 restricted CTL directed against HIV-1 peptides. However it is possible that the identification of protective HLA alleles or HLA restricted peptides in HIV-1 infected patients with a benign course of disease does not necessarily indicate that the same alleles or peptides are crucial for the design of a protective vaccine. Kaul and co-workers were able to show that CD8⁺ T cells from HIV-1 exposed but uninfected African women recognize different epitopes than CD8⁺ T cells from HIV-1 infected African women (49). This suggests that the epitopes that the immune system is directed against

during a natural infection might be different from those that are protective against infection.

HLA class II antigens are crucial for the development of an HIV-1 specific CD4⁺ T cell response. Rosenberg (1997) was the first to show that HIV-1 infected patients with a long-term non-progressive course of disease had HIV-1 specific CD4⁺ T cells that could proliferate against HIV-1 antigens (50). The identification of protective or unfavorable HLA class II alleles is less well elaborated on than the knowledge about protective HLA class I alleles. Cohorts of vertically infected children and HIV-infected adults demonstrate a protective effect of HLA DR13 (51).

The HIV-specific Cellular Immune Response

In comparison to HIV-1 infected patients with a rapid decline of CD4⁺ T cells, patients with a long-term non-progressive course of disease ("LTNP" = long-term non-progressors) have HIV-1-specific CTL precursors in high numbers and with a broad specificity towards various HIV-1 proteins. The different capacities of certain HLA alleles to present viral particles more or less efficiently and to induce a more or less potent immune response may explain why certain HLA alleles are associated with a more rapid or a slow progressive course of disease (see above).

Individuals have been described who developed CTL "escape" mutants after years of stable disease and the presence of a strong CTL response. The evolution of CTL escape mutants was associated with a rapid decline in CD4⁺ T cells in these patients, indicating the protective role of CTL (52).

HIV-specific CTL responses have been detected in HIV-1 exposed but uninfected individuals. Nef-specific CTL have been identified in HIV-1 negative heterosexual partners of HIV infected patients and env-specific CTL have been found in seronegative healthcare workers after exposure to HIV-1 containing material (needle stick injuries) (54).

The presence of a CTL response does not only correlate with the suppression of plasma viremia during the initial phase of HIV infection. Patients who underwent structured therapy interruptions, especially when HAART was initiated early following infection, demonstrated the appearance of HIV-specific CTL during the pauses.

However, it is still unclear in most patients who exhibit a potent temporary CTL response, why this CTL response diminishes later on. The appearance of viral "escape" mutants might explain why previously recognized epitopes are no longer immunodominant.

The *nef* protein may downregulate HLA class I antigens and therefore counteract the recognition of infected cells by CTL. In addition, the majority of infected individuals do show detectable CTL responses. It is unclear why they are unable to control the virus. Interestingly, CTL from HIV-infected patients shows a lack of perforin and an immature phenotype, even though the ability to secrete chemokines and cytokines is not impaired. It is possible that the CTL in most HIV-1 infected individuals, although detectable, may be functionally defective, and thus unable to completely clear the virus. CD8⁺ T cells may also become HIV infected, although this was not demonstrated for HIV-specific CD8⁺ T cells. It is unclear, whether CD8⁺ T cells might temporarily express CD4 and which chemokine co-receptors mediate infection of these CD8⁺ T cells.

In addition to the cytotoxic activities directed against HIV-infected cells, CD8⁺ T cells from HIV-1 infected patients exhibit a remarkable soluble HIV-1 inhibitory activity that inhibits HIV-1 replication in autologous and allogeneic cell cultures (55). Despite multiple efforts, the identity of this inhibitory activity ("CAF") has not been clarified, although chemokines, such as MIP-1 α , MIP-1 β , RANTES (24), IL-16 (56), the chemokine MDC (57) and defensins, may account for at least some of the inhibition.

The T_H1/T_H2 Immune Response

Depending on the secretion pattern of cytokines, CD4⁺ T cells may be differentiated into T_H1 and T_H2 cells. T_H1 CD4⁺ T cells primarily produce interleukin-2 (IL-2) and IFN γ , which represent the cytokines that support the effector functions of the immune system (CTL, NK-cells, macrophages). T_H2 cells predominantly produce IL-4, IL-10, IL-5 and IL-6, which represent the cytokines that favor the development of a humoral immune response. Since T_H1 cytokines are critical for the generation of CTLs, an HIV-1-specific T_H1 response is regarded as being a protective immune response. Studies on HIV-exposed but non-infected individuals have shown, that following in vitro stimulation with HIV-1 env antigens (gp120/gp160) and peptides, T cells from these individuals secrete IL-2 in contrast to non-exposed control persons (58). Similar studies were undertaken in healthcare workers after needlestick injuries and in newborns from HIV-infected mothers. Although these observations may indicate that a T_H1-type immune response is potentially protective, it should be considered that similar immune responses might also have been generated after contact with noninfectious viral particles and therefore do not necessarily imply a means of protection against a replication-competent virus.

HIV-1-specific Humoral Immune Responses

The association between an HIV-1 specific humoral immune response and the course of disease is less well characterized. A slow progression of immunodeficiency was observed in patients with high titers of anti-p24 antibodies (63), persistence of neutralizing antibodies against primary and autologous virus (64), and lack of antibodies against certain gp120 epitopes (62).

Long-term non-progressors with HIV tend to have a broad neutralizing activity towards a range of primary isolates and show persistence of neutralizing antibodies against autologous virus. At present, it is unclear whether the presence of neutralizing antibodies in LTNP represents part of the protection or whether

it merely reflects the integrity of a relatively intact immune system. Individuals that have a substantial risk for HIV-1 infection, but are considered "exposed, non-infected", by definition represent individuals with a lack of a detectable antibody response to HIV-1. This definition implies that a systemic humoral immune response may not represent a crucial protective mechanism. It has been shown that these individuals may demonstrate a local (mucosal) IgA response against HIV-1 proteins that are not detected by the usual antibody testing methods (65, 66). Thus, local IgA, rather than systemic IgG, may be associated with protection against HIV-1 infection. There is also some evidence that some anti-HIV-1 antibodies can enhance the infection of CD4⁺ T cells.

A number of old and recent studies have shown that neutralizing antibodies do exist in HIV-1 infected individuals; however, they seem to lag in time. That is, individuals will develop neutralizing antibodies to their own viruses with time, however, by the time these antibodies develop, the new viruses circulating in the individual's plasma will become resistant to neutralization, even though the older ones are now sensitive to the current antibodies in the patient's serum. Thus, the antibody response appears to be hitting a 'moving' target, allowing viruses to escape continuously. Further knowledge gained on understanding the mechanisms of humoral escape will likely lead to potential new therapies.

Improved knowledge and understanding of the pathophysiologic mechanisms during the course of HIV-1 infection have not only contributed to the development of antiretroviral treatment strategies, but have given rise to new therapeutic approaches, such as cytokine therapies, e.g., IL-2 and therapeutic vaccination. However, the most important challenge and thus, the demand for a better understanding of the immunopathogenesis of HIV-1 infection, remains the development of a protective vaccine, which is urgently needed to interrupt the epidemic especially in countries of the Sub Sahara and Southeast Asia.

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Chapter 2: Acute HIV-1 Infection

Marcus Altfeld and Bruce D. Walker

Introduction

Acute HIV-1 infection presents in 40 – 90 % of cases as a transient symptomatic illness, associated with high levels of HIV-1 replication and an expansive virus-specific immune response. With 14,000 new cases per day worldwide, it is an important differential diagnosis in cases of fever of unknown origin, maculopapular rash and lymphadenopathy.

The diagnosis of acute infection is missed in the majority of cases, as other viral illnesses (“flu”) are often assumed to be the cause of the symptoms, and there are no HIV-1-specific antibodies detectable at this early stage of infection. The diagnosis therefore requires a high degree of clinical suspicion, based on clinical symptoms and history of exposure, in addition to specific laboratory tests (detection of HIV-1 RNA or p24 antigen and negative HIV-1 antibodies) confirming the diagnosis.

An accurate early diagnosis of acute HIV-1 infection is important, as patients may benefit from therapy at this early stage of infection (see below), and infection of sexual partners can be prevented.

Signs and Symptoms

After an incubation period of a few days to a few weeks, most cases present with an acute flu-like illness. The most common symptoms (see Table 1) are fever, maculopapular rash, oral ulcers, lymphadenopathy, arthralgia, pharyngitis, malaise, weight loss, aseptic meningitis and myalgia. In a recently published study by Hecht et al., fever (80 %) and malaise (68 %) had the highest sensitivity for clinical diagnosis of acute HIV-1 infection, whereas loss of weight (86 %) and oral ulcers (85 %) had

the highest specificity. In this study, the symptoms of fever and rash (especially in combination), followed by oral ulcers and pharyngitis had the highest positive predictive value for diagnosis of acute HIV-1 infection. In another study by Daar et al., fever, rash, myalgia, arthralgia and night sweats were the best predictors for acute HIV-1 infection.

Table 1: Main symptoms of acute HIV-1 infection

Symptom	Frequency	Odds ratio (95% CI)
Fever	80%	5.2 (2.3-11.7)
Rash	51%	4.8 (2.4-9.8)
Oral ulcers	37%	3.1 (1.5-6.6)
Arthralgia	54%	2.6 (1.3-5.1)
Pharyngitis	44%	2.6 (1.3-5.1)
Loss of appetite	54%	2.5 (1.2-4.8)
Weight loss > 2.5 kg	32%	2.8 (1.3-6.0)
Malaise	68%	2.2 (1.1-4.5)
Myalgia	49%	2.1 (1.1-4.2)
Fever and rash	46%	8.3 (3.6-19.3)

From: Hecht FM et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS 2002, 16: 1119-1129

The symptomatic phase of acute HIV-1 infection lasts between 7 – 10 days, and rarely longer than 14 days. The severity and duration of symptoms has prognostic implications, as severe and prolonged symptoms are associated with more rapid disease progression. The nonspecific nature of the symptoms poses a great challenge to the clinician and underlines the importance of a detailed history of exposure.

Diagnosis

The diagnosis of acute HIV-1 infection is based on the detection of HIV-1 replication in the absence of HIV-1 antibodies, as these are not yet present at this early stage of infection. Different tests are available for diagnosis of acute HIV-1 infection.

The most sensitive tests are based on detection of plasma HIV-1 RNA.

In a recently published study, all assays for HIV-1 RNA that were tested (branched chain DNA, PCR and GenProbe) had a sensitivity of 100 %, but occasionally (in 2 – 5 % of cases) led to false positive results. False positive results from these tests are usually below 2,000 copies HIV-1 RNA per ml plasma, and therefore far below the high titers of viral load normally seen during acute HIV-1 infection (in our own studies on average 13×10^6 copies HIV-1 RNA/ml with a range of $0.25 - 95.5 \times 10^6$ copies HIV-1 RNA/ml). Repetition of the assay for HIV-1 RNA from the same sample with the same test led to a negative result in all false positive cases. Measurement of HIV-1 RNA from duplicate samples therefore results in a sensitivity of 100 % with 100 % specificity. In contrast, detection of p24 antigen has a sensitivity of only 79 % with a specificity of 99.5 – 99.96 %. The diagnosis of acute HIV-1 infection must be subsequently confirmed with a positive HIV-1 antibody test (seroconversion) within the following weeks.

During acute HIV-1 infection, there is frequently a marked decrease of CD4⁺ cell count, which later increases again, but usually does not normalize to the initial levels. In contrast, the CD8⁺ cell count rises initially, which may result in a CD4⁺/CD8⁺ ratio of < 1. Infectious mononucleosis is the most important differential diagnosis. Hepatitis, influenza, toxoplasmosis, syphilis and side effects of medications may also be considered.

In summary, the most important step in the diagnosis of acute HIV-1 infection is to include it in the differential diagnosis. The clinical suspicion of an acute HIV-1 infection then merely requires performance of an HIV-1 antibody test and possibly repeated testing of HIV-1 viral load, as shown in the algorithm in Figure 1 (adapted from Hecht et al., AIDS 2002).

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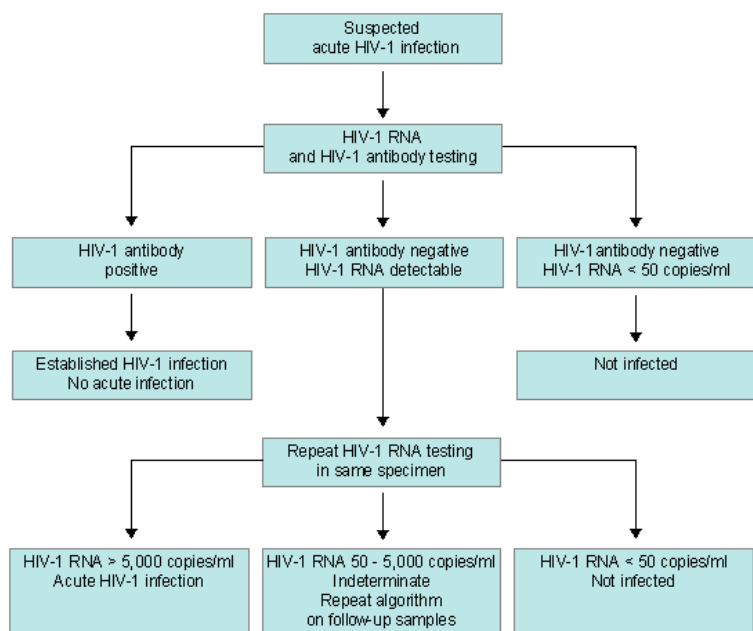


Figure 1

Treatment

The goal of antiretroviral therapy during acute HIV-1 infection is to reduce the number of infected cells, preserve HIV-1-specific immune responses and possibly lower the viral set point in the long term. Several studies in recent years have shown that treatment of acute HIV-1 infection allows long-term viral suppression, leads to preservation and even increase of HIV-1-specific T helper cell responses and allows for the conservation of a very homogeneous virus population.

First studies in patients who were treated during acute HIV-1 infection and subsequently went through structured treatment interruptions show that the HIV-1-specific immune response

could be boosted in these patients. Most patients were subsequently able to discontinue therapy and experienced at least temporal control of viral replication, with viral set points remaining below 5,000 copies/ml for more than 3 years in some patients. However, in a number of individuals viral load rebounded to higher level during longer follow-up, requiring the initiation of therapy.

The long-term clinical benefit of early initiation of therapy has not been demonstrated yet. It is also not known how long the period between acute infection and initiation of therapy can be without losing immunological, virological and clinical benefit. In view of all these unanswered questions, patients with acute HIV-1 infection should be treated in controlled clinical trials. If this is not possible, the option of standard first-line treatment should be offered and discussed. Usually, treatment continues for at least a year, followed by structured treatment interruptions within the framework of controlled studies. It is important during counseling to clearly indicate the lack of definitive data on clinical benefit and to address the risks of antiretroviral therapy and treatment interruptions, including drug toxicity, development of resistance, acute retroviral syndrome during viral rebound and HIV-1 transmission and superinfection during treatment interruptions.

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Chapter 3: HIV Therapy 2003

1. Perspective

Christian Hoffmann

The development of antiretroviral therapy has been one of the most dramatic progressions in the history of medicine. Few other areas have been subject to such fast- and short-lived trends. Those who have experienced the rapid developments of the last few years have been through many ups and downs:

The early years, from 1987-1990, brought great hope and the first modest advances using monotherapy (Volberding et al. 1990, Fischl et al. 1990). But, by the time the results of the Concorde Study had arrived (Hamilton et al. 1992, Concorde 1994), both patients and clinicians had plunged into a depression that was to last for several years. Zidovudine was first tested on humans in 1985, and introduced as a treatment in March 1987 with great expectations. Initially, at least, it did not seem to be very effective. The same was true for the nucleoside analogs zalcitabine, didanosine and stavudine, introduced between 1991 and 1994. The lack of substantial treatment options led to a debate that lasted for several years about which nucleoside analogs should be used, when, and at what dose. One such question was: Should the alarm clock be set to go off during the night for a sixth dose of zidovudine?

Many patients, who were infected during the early and mid-80s, began to die. Hospices were established, as well as more and more support groups and ambulatory nursing services. One became accustomed to AIDS and its resulting death toll. There was, however, definite progress in the field of opportunistic infections (OI) – cotrimoxazole, pentamidine, ganciclovir, foscarnet and fluconazole saved many patients' lives, at least in the short-term. Some clinicians started to dream of a kind of "mega-prophylaxis". But the general picture was still tainted by

an overall lack of hope. Many remember the somber, almost depressed mood of the IXth World AIDS Conference in Berlin, in June 1993. Between 1989 and 1994, morbidity and mortality rates were hardly affected.

Then, in September 1995, the preliminary results of the European-Australian DELTA Study (Delta 1995) and the American ACTG 175 Study (Hammer et al. 1996) attracted attention. It became apparent that combination therapy with two nucleoside analogs was more effective than monotherapy. Indeed, the differences made on the clinical endpoints (AIDS, death) were highly significant. Both studies demonstrated that it was potentially of great importance to immediately start treatment with two nucleoside analogs, as opposed to using the drugs “sequentially”.

This was by no means the final breakthrough. By this time, the first studies with protease inhibitors (PIs), a completely new drug class, had been ongoing for several months. PIs had been designed in the lab using the knowledge of the molecular structure of HIV and protease – their clinical value was initially uncertain. Preliminary data, and many rumors, were already in circulation. In the fall of 1995, a fierce competition started up between three companies: Abbott, Roche and MSD. The licensing studies for the three PIs, zidovudine, zalcitabine and didanosine, were pursued with a great amount of effort, clearly with the goal of bringing the first PI onto the market. The monitors of these studies in the different companies “lived” for weeks at the participating clinical sites. Deep into the night, case report files had to be perfected and thousands of queries answered. All these efforts led to a fast track approval, between December 1995 and March 1996, for all three PIs – first zidovudine, followed by zalcitabine and didanosine – for the treatment of HIV.

Many clinicians (including the author) were not really aware at the time of what was happening during these months. AIDS remained ever present. Patients were still dying, as only a relatively small number were participating in the PI trials – and very few were actually adequately treated by current standards.

Doubts remained. Hopes had already been raised too many times in the previous years by alleged miracle cures. Early in January 1996, other topics were more important: palliative medicine, treatment of CMV, MAC and AIDS wasting syndrome, pain management, ambulatory infusion therapies, even euthanasia.

In February 1996, during the 3rd Conference on Retroviruses and Opportunistic Infections (CROI) in Washington, many caught their breath as Bill Cameron reported the first data from the ABT-247 Study during the latebreaker session. The auditorium was absolutely silent. Riveted, listeners heard that the mere addition of ritonavir oral solution decreases the frequency of death and AIDS from 38 % to 22 % (Cameron et al. 1998). These were sensational results in comparison to everything else that had been previously published!

But for many, the combination therapies that became widely used from 1996 onwards, still came too late. Some severely ill patients with AIDS managed to recover during these months, but, even in 1996, many still died. Although the AIDS rate in large centers had been cut in half between 1992 and 1996 (Brodt et al. 1997), in smaller centers roughly every fifth patient died in this year.

However, the potential of the new drugs was slowly becoming apparent, and the World AIDS Conference in Vancouver a few months later, in June 1996, was like a big PI party. Even regular news channels reported in great depth on the new “AIDS cocktails”. The strangely unscientific expression “highly active antiretroviral therapy” (HAART) began to spread irreversibly. Clinicians were only too happy to become infected by this enthusiasm.

By this time, David Ho, Time magazine’s “Man of the Year” in 1996, had shed light on the hitherto completely misunderstood kinetics of HIV with his breakthrough research (Ho et al. 1995, Perelson et al. 1996). A year earlier, Ho had already initiated the slogan “hit hard and early”, and almost all clinicians were

now taking him by his word. With the new knowledge of the incredibly high turnover of the virus and the relentless daily destruction of CD4+ T cells, there was no longer any consideration of a “latent phase” – and no life without antiretroviral therapy. In many centers almost every patient was treated with HAART. Within only three years, from 1994-1997, the proportion of untreated patients in Europe decreased from 37 % to barely 9 %, whilst the proportion of HAART patients rose from 2 % to 64 % (Kirk et al. 1998).

Things were looking good. By June 1996, the first non-nucleoside reverse transcriptase inhibitor, nevirapine, was licensed, and a third drug class introduced. Nelfinavir, another PI, had also arrived. Most patients seemed to tolerate the drugs well. 30 pills a day? No problem, if it helps. And how it helped! The number of AIDS cases was drastically reduced. Within only four years, between 1994 and 1998, the incidence of AIDS in Europe was reduced from 30.7 to 2.5 per 100 patient years – i.e. to less than a tenth. The reduction in the incidence of several feared OIs, particularly CMV and MAC, was even more dramatic. HIV ophthalmologists had to look for new areas of work. The large OI trials, planned only a few months before, faltered due to a lack of patients. Hospices, which had been receiving substantial donations, had to shut down or reorientate themselves. The first patients began to leave the hospices, and went back to work; ambulatory nursing services shut down. AIDS wards were occupied by other patients.

In 1996 and 1997 some patients began to complain of an increasingly fat stomach, but was this not a good sign after the years of wasting and supplementary nutrition? Not only did the PIs contained lactose and gelatin, but the lower viremia was thought to use up far less energy. It was assumed that, because patients were less depressed and generally healthier, they would eat more. At most, it was slightly disturbing that the patients retained thin faces. However, more and more patients also began to complain about the high pill burden.

In June 1997, the FDA published the first warning about the development of diabetes mellitus associated with the use of PIs (Ault 1997). In February 1998, the CROI in Chicago finally brought home the realization among clinicians that protease inhibitors were perhaps not as selective as had long been believed. One poster after the next, indeed whole walls of pictures showed fat abdomens, buffalo humps, thin legs and faces. A new term was introduced at the beginning of 1998, which would influence the antiretroviral therapy of the years to come: lipodystrophy. And so the old medical wisdom was shown to hold true even for HAART: all effective drugs have side effects. The actual cause of lipodystrophy remained completely unclear. Then, in early 1999, a new hypothesis emerged from the Netherlands: “mitochondrial toxicity”. It has become a ubiquitous term in HIV medicine today.

The dream of eradication (and a cure), still widely hoped for in the beginning, eventually had to be abandoned, too. Mathematical models are evidently not suitable for predicting what will really happen. In 1997, it was still estimated that viral suppression, with a maximum duration of three years, was necessary; after this period, it was predicted that all infected cells would presumably have died. Eradication was the magic word. At every conference since then, the duration of three years has been adjusted upwards. Nature is not so easy to predict, and newer studies came to the sobering conclusion that HIV remains detectable in latent infected cells, even after long-term suppression. To date, nobody knows how long these latent infected cells survive, and whether even a small number of them would be sufficient for the infection to flare up again as soon as treatment is interrupted. Finally, during the Barcelona World AIDS Conference, experts in the field admitted to bleak prospects for eradication. The most recent estimates for eradication of these cells were approximately 50-70 years. One thing is certain: HIV will not be curable for at least the next 10 years.

Instead of eradication, it has become more realistic to consider the lifelong management of HIV infection as a chronic disease

in the future, similar to diabetes mellitus. This means, however, that drugs have to be administered over many years, which demands an enormous degree of discipline from patients. Those who are familiar with the management of diabetes understand the challenges that patients and clinicians have to face and how important it will be to develop better combinations in the coming years. Hardly anyone will have the discipline and ability, both mentally and physically, to take the currently available pills several times daily at fixed times for the next ten, twenty or even thirty years. But, presumably, this will not be necessary. There will be new and improved treatment regimens. Once-daily regimens are coming; maybe even twice-weekly.

At the same time, the knowledge of the risks of antiretroviral therapy has changed the approach of many clinicians towards treatment over the last three years. By the year 2000, many strict recommendations from previous years were already being revised. "Hit HIV hard, but only when necessary" is now heard more than "hit hard and early" (Harrington and Carpenter 2000). The simple question of "when to start?" is now being addressed at long symposia. It is often a question that requires great sensitivity.

Despite all the skepticism, it is important not to forget what HAART can do. HAART can often achieve miracles! Cryptosporidia and Kaposi's sarcoma simply disappear; PML may even be cured completely; secondary prophylaxis for CMV can be stopped; and above all: patients feel significantly better, even if some activists and AIDS counselors still do not want to admit this.

This also means, however, that many younger clinicians in Western countries who entered into HIV medicine at the end of the 90s often no longer know what AIDS really means. AIDS for them is an accident, whose damage can be fixed. They did not experience the "stone age" of AIDS.

HIV clinicians are well advised, perhaps more than other clinicians, to remember the "stone age", whilst still keeping an open

mind for new approaches. Those, who are strictly opposed to the interruption of treatment, and insistent on particular schemata of treatment, are not only overlooking the realities of treatment, but also losing touch. Those, who do not make an effort to broaden their knowledge several times a year at different conferences, will not be able to provide adequate treatment for their patients in a field that changes direction at least every two to three years. Those, who adhere strictly to evidence-based HIV medicine, and only treat according to guidelines, quickly become outdated. HIV medicine is ever changing. Treatment guidelines remain just guidelines. They are often out of date by the time of publication. There are no laws set in stone. However, those, who confuse therapeutic freedom with random choices and assume that data and results coming from basic research can be ignored, are also missing the point. Individualized treatment is not random treatment. In addition, it cannot be stressed enough, that clinicians are also responsible for the problem of bad compliance. Even if many experienced clinicians have come to disregard this: every patient has the right to know why he is taking which therapy or, indeed, why it has been omitted.

HIV remains a dangerous and cunning opponent. Patients and clinicians must tackle it together. The following describes how this can be done.

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2. Overview of Antiretroviral Drugs

Christian Hoffmann

Table 2.1: Antiretroviral agents

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)			
Trade name	Abb.	Drug	Manufacturer
Combivir [®]		AZT+3TC	GSK
Epivir [®]	3TC	Lamivudine	GSK
Hivid [®]	ddC	Zalcitabine	Roche
Retrovir [®]	AZT	Zidovudine	GSK
Trizivir [®]		AZT+3TC+ABC	GSK
Videx [®]	ddI	Didanosine	BMS
Viread [®]	TDF	Tenofovir	Gilead
Zerit [®]	d4T	Stavudine	BMS
Ziagen [®]	ABC	Abacavir	GSK
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Rescriptor [®]	DLV	Delavirdine	Pfizer
Sustiva [®] , Stocrin [®]	EFV	Efavirenz	BMS
Viramune [®]	NVP	Nevirapine	Boehringer Ingelheim
Protease Inhibitors (PIs)			
Agenerase [®]	APV	Amprenavir	GSK
Crixivan [®]	IDV	Indinavir	MSD
Fortovase [®]	SQV-SGC	Saquinavir soft gel	Roche
Invirase [®]	SQV-HGC	Saquinavir hard gel	Roche
Kaletra [®]	LPV	Lopinavir/ Ritonavir	Abbott
Norvir [®]	RTV	Ritonavir	Abbott
Viracept [®]	NFV	Nelfinavir	Roche

Three classes of antiretroviral agents are currently available for the treatment of HIV infection: nucleoside and nucleotide analogs (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Some 20 drug products have been licensed, including formulations of both individual and combined antiretroviral agents. The fusion inhibitor T-20 was launched in March 2003 as the prototype of a fourth drug class. A number of other drugs and new classes of drugs are in

the pipeline and expected to be licensed in the next years. Research is also focusing on immunomodulatory approaches with vaccines or cytokines (interferons, interleukins).

The following overview will deal mainly with the individual antiretroviral agents and their specific features and problems. Common combinations are described in the chapter on “How to start HAART?”.

Nucleoside Analogs (“nukes”, NRTIs)

Mechanism of action

Nucleoside analogs (slang: “nukes”) are also referred to as nucleoside reverse transcriptase inhibitors. Their target is the HIV enzyme reverse transcriptase. Acting as alternative substrates or “false building blocks“, they compete with physiological nucleosides, differing from these only by a minor modification in the sugar (ribose) molecule. The incorporation of nucleoside analogs aborts DNA synthesis, as phosphodiester bridges can no longer be built to stabilize the double strand.

Nucleoside analogs are converted to the active metabolite only after endocytosis, whereby they are phosphorylated to triphosphate derivatives. AZT and d4T are thymidine analogs, ddC and 3TC are cytidine analogs. A combination of AZT and d4T would be senseless, since both drugs compete for the same bases; this also applies to ddC and 3TC. ddI is an inosine analog, which is converted to dideoxyadenosine; abacavir is a guanine analog. There is a high degree of cross-resistance between nucleoside analogs (see also the chapter on “Resistance“).

Nucleoside analogs are important components of almost all combination regimens. They are potent inhibitors of HIV replication, and are rapidly absorbed when taken orally. However, they can cause a wide spectrum of side effects, encompassing myelotoxicity, lactic acidosis, polyneuropathy and pancreatitis. Complaints include fatigue, headache and a variety of gastrointestinal problems such as abdominal discomfort, nausea, vomiting and diarrhea. Although lipodystrophy was initially linked

exclusively to treatment with protease inhibitors, numerous disorders of lipid metabolism (especially lipoatrophy) are now also attributed to nucleoside analogs (Galli et al. 2002).

Most side effects are probably related to mitochondrial toxicity, first described in 1999 (Brinkmann et al. 1999). Mitochondrial function also requires nucleosides. The metabolism of these important organelles is disrupted by the incorporation of false nucleosides, leading to mitochondrial degeneration. More recent clinical and scientific data indicates that there are probably significant differences between individual drugs with regard to mitochondrial toxicity.

Nucleoside analogs are eliminated mainly by renal excretion and do not interact with drugs that are metabolized by hepatic enzymes. There is therefore little potential for interaction. However, substances such as ribavirin may decrease the intracellular phosphorylation of AZT or d4T in vitro (Piscitelli et Galliciano 2001).

Individual agents: Special features and problems

Abacavir (Ziagen[®]) is a potent and mostly well-tolerated nucleoside analog with good CNS penetration. One drawback to the use of abacavir is the occurrence of the hypersensitivity reaction (HSR), which is not yet fully understood. HSR occurs in approximately 4-5% of patients, almost always (93%) within the first six weeks of treatment. Every treating physician should be familiar with this syndrome, which can be fatal in individual cases, especially after rechallenge (see Management of Side Effects). The combination of strongly worded warnings contained in the package insert and the often unspecific symptoms of the HSR poses a constant challenge to the patient-physician relationship. Several reports were published in 2002 suggesting that patients with HLA type B5701 may be genetically predisposed and at higher risk than others (Mallal et al. 2002, Hetherington et al. 2002). Apart from HSR, abacavir seems to have an otherwise favorable long-term profile, especially in terms of mitochondrial toxicity (Carr et al. 2002).

AZT – Zidovudine (Retrovir[®]) was the first antiretroviral agent to be put on the market, in 1987. In the first few years, it was administered in doses that were too high, which led to significant myelotoxicity and brought the drug into somewhat of disrepute. Even with the standard doses given today, monitoring of blood count is obligatory. Long-term treatment almost always increases MCV. Initial gastrointestinal complaints may present a short-term problem. AZT seems to have a more favorable profile with regard to long-term toxicity. Lack of neurotoxicity and good CNS penetration are important advantages of this drug, which has remained the cornerstone of many HAART regimens and transmission prophylaxis.

ddC - Zalcitabine (Hivid[®]) was investigated closely in the double nuke studies of the early to mid-nineties. It has since been marginalized due to the relatively frequent development of peripheral neuropathy, the three times daily dosing requirement, and lack of data in the HAART era. At the present time, ddC is by far the least used nucleoside analog. Stomatitis is a side effect that is relatively specific for ddC. Although a twice daily dose now seems possible (Moyle and Gazzard 1998), increased competition from newer nucleoside analogs may mean that this substance will disappear from antiretroviral therapies.

ddI – Didanosine (Videx[®]) is a nucleoside analog that has been well investigated and shown good efficacy in numerous randomized studies. The introduction of acid-resistant tablets in 2000, to replace the chewable tablets used for many years, has done much to improve tolerability. ddI remains one of the most important components of many HAART regimens. ddI was shown to be more potent than AZT, even with regard to disease progression in the ACTG 175 Study (Hammer et al. 1996), confirming results of an earlier study (Kahn et al. 1992). After failure with AZT, ddI is probably more effective than d4T (Havlir et al. 2001). Gastrointestinal complaints are typical and relatively frequent side effects. Pancreatitis, a less common but also typical adverse effect, may be fatal in individual cases and is possibly dose-related. Special caution should be given to the

combination with d4T and hydroxyurea (Havlir et al. 2001). The advantage to the use of ddI of simple once daily dosing, which is possible due to the long intracellular half-life, is counterbalanced by the need to take the drug under fasting conditions.

d4T – Stavudine (Zerit®) was the second thymidine analog to be introduced after AZT. On initiation of therapy it is often better tolerated than AZT, producing less gastrointestinal side-effects and limited myelotoxicity. It is definitely just as effective and was for many years the most frequently prescribed antiretroviral agent. Recently, focus on long-term toxicity rather than efficacy has revealed that d4T seems to be associated with more problems than other nucleoside analogs. It increases the risk of lactic acidosis and hyperlactacidemia, especially in combination with ddI or 3TC (Gerard et al. 2000, Miller et al. 2000, Mokrzycki et al. 2000, John et al. 2001). There has also been concern over recent reports of progressive neuromuscular weakness. 22 of 25 patients (7 fatal cases), presenting with symptoms similar to the Guillain-Barré syndrome and with hyperlactacidemia, had received d4T, 11 of these d4T+ddI (Marcus et al. 2002). Lipodystrophy is probably also more frequent with d4T. In a German cohort the risk of lipoatrophy had doubled after one year of treatment (Mauss et al. 2002); in a Swiss cohort it had tripled after two years (Bernasconi et al. 2002). Other data, with one exception (Bogner et al. 2001), points in the same direction (Chene et al. 2002).

Even more significant than the data from cohort studies is the publication of the first studies showing the positive effect on lipoatrophy of discontinuation of d4T (and replacement with other nukes): In a randomized study from Australia, in which 111 lipoatrophic patients on stable HAART had d4T or AZT replaced either with abacavir or not, most benefit was seen in the d4T group (Carr et al. 2002). The effect at 24 weeks, however, was still very moderate. The increased subcutaneous fat tissue detectable by dEXA scan was not visible clinically. It may therefore take years, as the authors concluded, for lipoatrophy

to visibly improve after discontinuation of d4T. A positive effect, albeit once again weak, has been described in two further d4T-replacement studies (John et al. 2002, McGomsey et al. 2002). Thus, bearing resistance patterns in mind, in patients on d4T with severe lipoatrophy, the drug should be replaced, optimally with abacavir. There is, however, no assurance for resolution of lipoatrophy, and, above all, great patience is required.

3TC – Lamivudine (Epivir®) is a very well tolerated nucleoside analog. This substance is frequently used, as it is a component of both Combivir and Trizivir. Its main disadvantage is rapid development of resistance, and a single point mutation (M184V) is sufficient for loss of effectiveness. Since resistance is likely to develop after only a few weeks, 3TC has practically no effect as monotherapy. Thus, treatment with 3TC as the only nucleoside analog component of a combination is considered problematic. As the M184V mutation seems to impair viral fitness, however, continuation of 3TC therapy following this mutation may make good sense (Miller et al. 2002).

3TC is also effective against hepatitis B viruses. Once daily dosing appears to be feasible (Sension et al. 2002). In the US, 3TC has already been approved as the first once-daily nucleoside analog.

Tenofovir (Viread®) acts as a false building block similarly to nucleoside analogs, targeting the enzyme reverse transcriptase. However, in addition to the pentose and nucleic base it is monophosphorylated, and is therefore referred to as a nucleotide analog. The more accurate description of the substance is tenofovir DF (disoproxil fumarate), which is a phosphonate from which the phosphonate component is only removed by a serum esterase and which is activated intracellularly in two phosphorylation steps (Robbins et al. 1998).

After the first nucleotide analog adefovir was abandoned in HIV therapy due to weak antiviral activity and severe side effects (and is now being further developed in lower doses as the hepatitis B medication Hepsera®), tenofovir has shown mark-

edly improved tolerability and would also appear to be more potent. In the 902 Study, in which tenofovir versus placebo was added to HAART, tenofovir decreased viral load by 0.62 log after 48 weeks (Schooley et al. 2002). The 903 Study was a double-blind study in which treatment-naïve patients were given tenofovir or d4T (in addition to the backbone regimen with 3TC and efavirenz). Preliminary results showed at least equivalent potency (Staszewski et al. 2002). Tolerability was higher in the tenofovir group, especially with regard to polyneuropathy and fat redistribution. This is consistent with in vitro data, which shows that phosphorylated tenofovir has a low affinity for mitochondrial polymerases (Suo 1998).

Despite all the positive reports, long-term data on tenofovir are not yet available. In combination with ddI, there are increased levels of ddI, which could lead to increased toxicity (Kearney et al. 2002); a daily dose reduction of ddI to 250 mg is probably necessary. On the other hand, since tenofovir is eliminated renally, interactions with substances metabolized in the liver are rare. Longterm, the possibility of cumulative nephrotoxicity needs to be clarified.

Efficacy – Which nuke backbone is best?

All classical HAART regimens contain two nucleoside analogs as the “backbone” of treatment. For many years, numerous studies, especially before the introduction of PIs and NNRTIs, concentrated on the optimal combination of two nucleoside analogs.

There are probably no great differences. Although data has been contradictory, this is probably due to different study settings and frequently heterogeneous patient populations. There seems only to be consensus that ddC-containing nuke combinations are slightly less potent. A meta-analysis of several randomized studies has shown that AZT+ddI is more potent than AZT+ddC (HTCG 1999). Similarly, in patients pretreated with monotherapy, AZT+3TC was superior to AZT+ddC (Bartlett et al. 1996).

AZT+3TC or d4T+ddI?

A great deal of data is now available comparing the two most frequent combinations – AZT+3TC and d4T+ddI. In the French Albi Trial, d4T+ddI was clearly more effective than AZT+3TC. However, it was later shown that d4T+ddI significantly caused more frequent lipodystrophy (Molina et al. 1999, Chene et al. 2002), and following failure of d4T+ddI, AZT resistance was found to be equal or more than that with AZT+3TC (Picard et al. 2001). The combination with indinavir also showed a positive trend in favor of d4T+ddI over AZT+3TC (Eron et al. 2000).

These results, however, were not confirmed in another study (Carr et al. 2000). Similarly, no difference in efficacy was found between d4T+ddI, AZT+3TC and d4T+3TC, whether in combination with nevirapine or indinavir (Foudraine et al. 1998, Squire et al. 2000, French et al. 2002).

Although ACTG 384, the ultimate large study dealing with this issue has yet to be completed, the pendulum seems to have swung in favor of AZT+3TC. Preliminary results, presented recently at the World AIDS Conference in Barcelona (Robbins et al. 2002, Shafer et al. 2002), were puzzling: AZT+3TC is virologically superior to d4T+ddI, although only in combination with efavirenz; a combination with nelfinavir shows no added benefit. A plausible explanation has yet to be given.

Summary of nuke backbones

To date, the results of efficacy studies remain inconclusive and do not provide a mandate for the choice of one particular combination over another. Treatment can thus be adapted to the particular needs of each patient.

Choice of one of the three combinations AZT+3TC, AZT+ddI or d4T+3TC is nearly always appropriate. In view of recent studies on lactic acidosis and lipodystrophy, the combination of d4T+ddI should be carefully considered and monitored.

Other combinations such as AZT+ABC, d4T+ABC, ABC+3TC, or ddI+3TC also seem acceptable, but are not as well supported by clinical data. ddI+3TC may also produce less favorable results than AZT+3TC or d4T+3TC, as was suggested by the ACTG 306 Study (Kuritzkes et al. 1999).

Combinations such as AZT+d4T, ddC+3TC, d4T+ddC and ddI+ddC should definitely be avoided. It has also been shown that constant changing of the nuke backbone with the goal of preventing development of resistance has no positive effect and probably only confuses the patient (Molina et al. 1999).

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Mechanism of action and efficacy

As with the nucleoside analogs, the target enzyme of NNRTIs is reverse transcriptase. NNRTIs were first described in 1990. In contrast to the NRTIs, they are not “false” building blocks, but rather bind directly and non-competitively to the enzyme, at a position in close proximity to the substrate-binding site for nucleosides. The resulting complex blocks the catalyst-activated binding site of the reverse transcriptase, which can thus bind fewer nucleosides, and polymerization is slowed down significantly. In contrast to NRTIs, NNRTIs do not require activation within the cell.

The three currently available NNRTIs – nevirapine, delavirdine and efavirenz – were introduced between 1996 and 1998. Having only limited potency as individual agents, they were initially regarded somewhat skeptically. Although studies such as the INCAS Trial or Protocol 0021II clearly demonstrated the superiority of triple therapy with nevirapine or delavirdine compared to double nuke therapy (Conway et al. 2000), the “rise” of the NNRTIs was rather hesitant, and did not receive the media attention given to that of the PIs.

Since then, both randomized and large cohort studies have demonstrated that NNRTIs are extremely effective in combina-

tion with nucleoside analogs. The immunological and virological potency of NNRTIs is at least equivalent to that of PIs (Friedl et al. 2001, Staszewski et al. 1999, Torre et al. 2001). In contrast to PIs, however, the clinical effect has not yet been proven, as the studies that led to licensing of NNRTIs all used surrogate markers. Nevertheless, the simple dosage and the overall good tolerability have led nevirapine and efavirenz to become important components of HAART regimens, which are often even ranked above those containing PIs. While the manufacturers of nevirapine and efavirenz compete for market domination, delavirdine has lost relevance (a situation which is unlikely to change).

To date, no controlled study provides clear evidence that one NNRTI is more potent than another. A small, randomized pilot study from Spain demonstrated no significant differences between nevirapine and efavirenz (Nunez et al. 2002). However, several cohort studies indicate the superiority of efavirenz. In an Italian study, treatment failure on nevirapine was 2.08 times more likely than on efavirenz (Cozzi-Lepri et al. 2002), and in the Euro-SIDA study this factor was 1.75 (Phillips et al. 2001). Such analyses should be interpreted with caution, as extremely heterogeneous patient groups, with varying previous treatments, were studied. This was recently underlined by the eagerly awaited results of the 2NN Study ("The Double Non-Nucleoside Study"). 2NN is the first large-scale randomized trial directly comparing nevirapine and efavirenz-containing regimens in HAART-naïve patients. The trial showed that nevirapine and efavirenz were comparable with respect to virological and immunological efficacy after 48 weeks of therapy. However, nevirapine and efavirenz have distinctive adverse event profiles which should be considered in the choice of these drugs (see below).

In the case of both NNRTIs, efficacy and toxicity probably correlate with plasma levels (Veldkamp et al. 2001, Marzolini et al. 2001, Gonzalez et al. 2002). Nevirapine and efavirenz are metabolized by cytochrome P450 enzymes (Miller et al. 1997).

Nevirapine is an inductor, whereas efavirenz is both an inductor and an inhibitor of the cytochrome P450 isoenzyme. The combination of efavirenz with saquinavir or lopinavir leads to strong interactions that require dose adjustments.

Individual agents: Special features and problems

The most significant problem with NNRTIs is resistance, with a high risk of cross-resistance. One point mutation on position 103 (K103N) of the hydrophobic binding site is sufficient to eliminate an entire class of drug. Point mutations may occur very rapidly. Resistance has even been described in maternal transmission prophylaxis, in mothers who had taken nevirapine only once during delivery (Eshleman et al. 2002). Thus, NNRTI-containing regimens are vulnerable – and waiting too long to switch therapy during insufficient suppression of viral load almost certainly leads to complete resistance.

The side effects of nevirapine and efavirenz are quite different, and should be considered in the choice of regimen.

Nevirapine (Viramune®) was the first licensed NNRTI. In rare cases, it may cause serious hepatic toxicity. To prevent allergic reactions, the currently recommended dosage regimen is 200 mg qd for 2 weeks, followed by 200 mg bid thereafter. During the first 8 weeks, biweekly monitoring of liver function tests is recommended. A rash develops in 15-20 % of cases and leads to discontinuation in 7% of patients (Miller et al. 1997). In the case of an isolated rash or isolated elevation of transaminases (up to five times the upper limit of normal), treatment may usually be continued. However, treatment should be discontinued in the case of a rash with even slightly elevated transaminases (>2-fold of norm). Patients with chronic hepatitis are probably at a higher risk (Sulkowski et al. 2000). Similarly, there seems to be a correlation with plasma levels (Gonzalez et al. 2002). It is important to note that hepatic toxicity may occur even after several months (Sulkowski et al. 2002).

In contrast, nevirapine has a good lipid profile. In the Atlantic Study, in which nevirapine was tested against lamivudine and

indinavir, with all groups on a d4T+ddI backbone, those receiving nevirapine showed favorable lipid changes for cholesterol and triglycerides. Astonishingly, there was an increase in HDL (Van der Valk et al. 2001), demonstrated also in the Spanish Lipnefa Study (Fisac et al. 2002). These effects are undoubtedly positive. Whether they will have clinical relevance over time, remains to be seen.

Efavirenz (Sustiva[®], Stocrin[®]) was the third NNRTI to be approved and the first in which it was demonstrated that NNRTIs were at least as effective as PIs (Staszewski et al. 1999). The long half-life allows for once-daily dosing. With the approval of a new 600 mg capsule, dosage has been reduced to a single capsule per day.

Efavirenz may cause mild CNS side effects and should therefore be taken in the evening. These disorders usually include morning dizziness and somnolence; nightmares may also occur. The side effects probably correlate with high plasma levels (Marzolini et al. 2001). In one study, after four weeks of treatment with efavirenz, 66 % of patients complained of dizziness, 48 % of abnormal dreams, 37 % of somnolence and 35 % of insomnia. Although these symptoms seem to resolve with further treatment (frequencies of these complaints at 24 weeks was only 13 %, 18 %, 13 % and 7 %, respectively), patients must be warned of these potential side effects (Fumaz et al. 2002). To date, little is known of the effect on driving. We recommend that efavirenz should not be prescribed to patients during examination periods, to pilots or crane operators. Patients with impaired concentration should avoid potentially hazardous activities such as driving or operating heavy machinery (see package insert). Efavirenz is contraindicated in pregnancy. Lipids are not as favorably affected as with nevirapine (Hoffmann et al. 2000), but hepatotoxicity is less frequent.

Delavirdine (Rescriptor[®]): Due to a high pill burden and the required three times daily dosing, delavirdine is currently rarely prescribed, although it is likely to be approximately as effective as nevirapine and efavirenz (Wood et al. 1999, Conway 2000).

The need for prescription should be carefully considered. In 1999, an application for licensure in Europe was rejected due to insufficient efficacy data.

Protease Inhibitors (PIs)

Mechanism of action and efficacy

The HIV protease cuts the viral gag-pol polyprotein into its functional subunits. Inhibition of the protease, preventing proteolytic splicing and maturation, leads to the release of virus particles which are unable to infect new cells. With knowledge of the molecular structure of the protease encoded by the virus, the first protease inhibitors were designed in the early nineties; these substances were modified in such a way, that they fit exactly into the enzyme active site of the HIV protease (detailed reviews: Deeks 1997, Somadossi 1999, Eron 2001).

Since 1995, protease inhibitors have revolutionized the treatment of HIV infection (see also the chapter on “History”). At least three large studies with clinical endpoints proved the efficacy of indinavir, zidovudine and zalcitabine (Hammer et al. 1997, Cameron et al. 1998, Stellbrink et al. 2000). Even if in recent years PIs have demonstrated a series of drawbacks, they remain an essential component of HAART, especially for treatment-experienced patients.

As with the NNRTIs, there has been intense pharmaceutical company competition to establish which PI has superior efficacy. However, comparative studies have failed to demonstrate clear superiority of one protease inhibitor over any other.

Two exceptions have to be mentioned: the hard gel capsule saquinavir-HGC and ritonavir. A large retrospective analysis has shown the relative benefit of indinavir when compared to saquinavir-HGC. There was significantly less virologic failure in patients taking indinavir (Fätkenheuer et al. 1997). In the Euro-SIDA cohort there was even a clinical benefit of indinavir when compared to saquinavir hard gel capsules (Kirk et al. 2001). Saquinavir was subsequently “rescued” mainly by

boosting (see below), but also by the development of soft gel capsules with improved resorption. A small, randomized study showed no differences between indinavir, saquinavir soft gel capsules, zidovudine, zalcitabine and didanosine, when combined with abacavir (McMahon et al. 2001). Similarly, the CHEESE Study found no differences between saquinavir-SGC and indinavir (Cohen et al. 1999).

In the case of zidovudine, the main problem is poor tolerability. In an open-label randomized trial with three groups, although no major differences could be shown between zidovudine/saquinavir and indinavir-containing regimens, but there was a definite unfavorable trend for patients on zidovudine, due not to virologic failure but to frequent discontinuation because of side effects (Katzenstein et al. 2000).

Boosted PI regimens are presumably more effective. Lopinavir/r in combination with d4T/3TC was shown to reduce viral load more effectively than zidovudine-containing HAART. After one year in the double-blind M98-863 Study, 67 % versus 52 % had a viral load below 50 copies/ml (Walmsley et al. 2002).

Individual agents: Special features and problems

Apart from gastrointestinal side effects and high pill burden, all PIs used in long-term therapy can be implicated in lipodystrophy and dyslipidemia (see also the chapter on “Lipodystrophy”; review in Graham 2000). Smaller randomized studies have shown that elevation of lipid levels is more pronounced in zidovudine-containing regimens than with saquinavir or zidovudine (Rogge et al. 2001, Wensing et al. 2001). In addition, there may be significant drug interactions with zidovudine and with boosted regimens. Sexual dysfunction has also been attributed to PIs (Schrooten et al. 2001), although data is inconclusive (Lallemand et al. 2002).

There is a high degree of cross-resistance between protease inhibitors, which was described even before PIs were put on the market (Condra et al. 1995; see also the chapter on “Resistance”). All PIs are inhibitors of the CYP3A4 system and inter-

act with numerous other drugs. Ritonavir is by far the strongest inhibitor, saquinavir probably the weakest.

Amprenavir (Agenerase[®]) – As an unboosted PI, the substance is hardly acceptable today due to the high pill burden (8 pills BID). Important side effects include gastrointestinal disorders and, in contrast to other PIs, occasional rashes. Whether the incidence of lipodystrophy and dyslipidemia is reduced as compared with other PIs has yet to be proven (Noble et al. 2000). The resistance profile of the drug is particularly interesting, as it only partially overlaps with that of other PIs. It is to be expected that Agenerase[®] will be removed from the market as soon as the follow-on drug fos-amprenavir is available. This could lead to serious competition for lopinavir in the area of salvage therapy.

Indinavir (Crixivan[®]) has been shown to be a very effective PI in numerous studies; it is probably the most extensively tested (Gulick et al. 1997, Hammer et al. 1997). The large amount of data is currently the most important argument in favor of this drug. Low protein binding (60 %) seems to allow better CNS penetration than with other PIs (Martin et al. 1999). Whether this is clinically significant remains to be seen.

There are, however, a number of problems associated with indinavir. First, it causes nephrolithiasis in approximately 5-10 % of patients and thus requires good hydration (at least 1.5 liters daily). Patients with a history of nephrolithiasis or renal insufficiency should therefore not receive indinavir. Secondly, in the unboosted form, indinavir must be taken three times daily in fasting conditions, a form of dosing that is currently unacceptable. Finally, the minimal inhibitory concentration is often reached as soon as 8 hours after administration.

Unboosted twice-daily dosing is not possible. A trial using 2 x 1200 mg indinavir (3 tablets BID) in 87 patients had to be stopped because of 36 % versus 9 % treatment failures in the study group with twice-daily dosing (Haas et al. 2000). For this reason, indinavir is increasingly being used in combination with

boosting doses of ritonavir. Such boosting may, however, present some problems due to side effects (Gatell et al. 2000, Harley et al. 2001, Shulman et al. 2002). In the MaxCmin1 Trial the drop-out rate in the indinavir group was clearly higher than among patients receiving saquinavir (Gerstoft et al. 2002). There are relatively frequent mucocutaneous side effects, reminiscent of retinoid therapy: alopecia, dry skin and lips, ingrown nails. Some patients may also develop asymptomatic hyperbilirubinemia.

Lopinavir/Ritonavir (Lopinavir/r, Kaletra[®]) is the newest PI and the first to contain a fixed booster dose of ritonavir, which may increase concentrations of lopinavir by more than 100-fold (Sham et al. 1998). Lopinavir has the highest genetic barrier of all PIs (6-8 cumulative PI resistance mutations are probably necessary for treatment failure), and it has surprising efficacy in salvage therapy. However, use in early treatment is controversial, and to date it has also not been shown whether lopinavir is the most effective PI for treatment-naïve patients. It is probably superior to nelfinavir (and also atazanavir), but as yet there is no data for boosted PIs such as indinavir, saquinavir or amprenavir. Dyslipidemia appears to be a significant problem with lopinavir therapy.

Nelfinavir (Viracept[®]) was the fourth PI to be put on the market and was for a long time one of the most frequently used PIs. Although it is also licensed for the (initially developed) dose of 3 x 3 capsules, nelfinavir may be taken twice daily in the dose of 2 x 5 capsules. Boosting with ritonavir does not lead to significant improvement in plasma levels.

The most frequent side effect of nelfinavir is diarrhea, which may be quite severe. The antiretroviral potency of nelfinavir is weaker than that of boosted PIs (Walmsley et al. 2002). In the large Agouron 511 Study which led to licensing, 61 % of patients (with an AZT+3TC backbone) showed blood levels under 50 copies/ml at 48 weeks (Saag et al. 2001). The substance has a good resistance profile. The D30N primary mutation for nelfinavir reduces viral fitness (Martinez et al. 1999) and does not

influence the efficacy of other PIs. Unfortunately however, other mutations, which in contrast can jeopardize the success of later regimens, also occur frequently. A new formulation enabling a reduction to 2 x 2 capsules daily is in development, which may reverse the recent downward trend in sales of nelfinavir due to strong competition.

Ritonavir (Norvir®) was the first PI for which efficacy was proven with clinical endpoints (Cameron et al. 1998). Due to its poor tolerability (gastrointestinal complaints, perioral paresthesias), ritonavir is generally no longer used as a single PI. However, when used to boost other protease inhibitors, the ritonavir dose can be reduced to 2 x 100 mg, whereby toleration is vastly improved. Ritonavir is a potent inhibitor of the cytochrome P450 pathway with a great potential for interactions with other drugs; thus, many drugs are contraindicated for concomitant administration with ritonavir. Metabolic disorders are probably more frequent than with other PIs. Caution should generally be exercised in patients with impaired liver function. It is important to inform patients that ritonavir capsules must be stored at cool temperatures, which can become a problem during long trips.

Saquinavir (Invirase® and Fortovase®) is the only PI which is available in two formulations: a hard gel capsule (Invirase® or saquinavir-HGC) and a soft gel capsule (Fortovase® or saquinavir-SGC). The soft gel capsules have a greatly improved bioavailability and therefore a superior antiviral activity, which was demonstrated in a pilot study in naive patients (Mitsuyasu et al. 1998). However, in the era of boosting with ritonavir, this distinction is probably less relevant (see below).

Saquinavir was the first PI to be licensed in December 1995 for HIV therapy. Although rare serious side effects can occur, the main adverse reactions are relatively mild gastrointestinal complaints, which are more frequent with the soft gel capsules (Kurovski et al. 2002). Saquinavir is otherwise well tolerated. In the MaxCmin1 Trial, the drop-out rate was significantly lower when compared to the indinavir group (Gerstoft et al. 2002).

Why “boost” PI regimens?

Ritonavir is a very potent inhibitor of the isoenzyme 3A4, a subunit of the cytochrome P450 hepatic enzyme system, and small doses of ritonavir lead to increased plasma levels (boosting) of almost all PIs (Kempf et al. 1997). Indeed, nelfinavir is the only drug for which boosting with ritonavir is not recommended, as plasma levels do not rise significantly (Kurowski et al. 2002).

The interaction between ritonavir and the other PIs simplifies the daily regimen by reducing the number of pills to be taken every day. Some PIs can now be used in twice-daily regimens. Recent trials are investigating the possibility of once-daily dosing. Boosting also aims to intensify therapy; due to the elevated plasma levels, boosted indinavir or amprenavir seem to be effective against resistant viral strains (Condra et al. 2000).

There is, however, a high degree of variability of boosted plasma levels among individuals. Therapeutic drug monitoring is therefore recommended (Burger et al. 2002). In addition to achieving elevated trough levels of the boosted drug, which prevents plasma levels from dropping below the minimal inhibitory concentration, ritonavir also increases peak levels, which may lead to more side effects.

Saquinavir/ritonavir is the most-studied booster combination regimen. Due to the low oral bioavailability of saquinavir, this combination was tested very early on. Plasma levels of saquinavir can be increased 20-fold by ritonavir. Studies have shown that the booster combination 400/400 (= 400 mg saquinavir plus 400 mg ritonavir, both twice daily) is virologically the most effective (Cameron et al. 1999). In patients already taking saquinavir, boosting may have only moderate effects (Smith et al. 2001). Boosting of saquinavir in the better tolerated 1000/100 combination has recently been licensed.

When boosting saquinavir, it is worth considering using Invirase[®] instead of Fortovase[®]. In a recently published study (Kurowski et al. 2002), boosted levels of saquinavir were even

higher for Invirase[®], which is also better tolerated with respect to gastrointestinal complaints than the subsequently developed Fortovase[®]. Interestingly, Invirase[®] is nearly twice as expensive as Fortovase[®] – an issue that the manufacturer Hoffmann-La Roche might well have to address in the near future, if, as can be expected, it comes under pressure from patient advocacy groups.

Table 2.2: Well investigated boosted PI regimens

	Dose in mg	Pills/day	Comment
Saquinavir/ Ritonavir	2 x 1000/100	2 x 6	Officially licensed for boosting
Saquinavir/ Ritonavir	2 x 400/400	2 x 6	Good efficacy, but problematic due to increased rate of side effects
Indinavir/ Ritonavir	2 x 800/100	2 x 3	Higher rate of nephrolithiasis (?)
Indinavir/ Ritonavir	2 x 400/400	2 x 5	Good pharmacokinetic data
Lopinavir/ Ritonavir	2 x 400/100	2 x 3	Only fixed combination in one capsule
Nelfinavir/ Ritonavir			Not recommended
Saquinavir/ Nelfinavir	3 x 600/750	3 x 6	Only well documented booster combination without ritonavir, but too many pills three times a day
Amprenavir/ Ritonavir	2 x 600/100	2 x 5	FDA approved

The combination of **indinavir/ritonavir** is also well investigated. There is good pharmacokinetic data for the 800/100 dose (Van Heeswijk et al. 1999). In a smaller pilot study with this combination, however, results showed nephrolithiasis in 19/57 patients (Voigt et al. 2001). The 400/400 dose presumably induces less renal side effects. The combination of indinavir/ritonavir seems to be associated with an increased risk of side effects. In studies such as BEST or NICE, switching from indinavir to indinavir/ritonavir was shown to have a slightly

higher rate of side effects and drop-outs (Gatell et al. 2000, Harley et al. 2001, Shulman et al. 2002).

Lopinavir/ritonavir is to date the only fixed booster combination therapy available in one capsule (see above). There is good data for **amprenavir/ritonavir**, especially for salvage therapy (Condra 2000, Duval et al. 2002). The FDA approved once daily dosing for this combination in 2002.

Boosted PIs are probably equivalent with regard to anti-HIV potency, although only sparse clinical data is as yet available. In the randomized MaxCmin1 Trial, efficacy of saquinavir and indinavir was comparable. The drop-out rate in the indinavir group was significantly higher, and was probably due to a higher incidence of side effects (Gerstoft et al. 2002). Results are expected to be published soon of a second trial, the MaxCmin2 Study, in which both treatment-naïve and treatment-experienced patients were randomized to receive either saquinavir/ritonavir or lopinavir/r. Interim analyses have shown that both combinations have good efficacy and exhibit no great differences (Dragstedt et al. 2002). Publication of the final data is expected in the third quarter of 2003.

Plasma levels even of well-boosted PIs seem to decrease with duration of treatment. After 10 months, saquinavir levels had dropped by 40 % in six patients (Gisolf et al. 2000). Plasma levels must therefore be monitored for all booster combinations, especially in patients with underlying liver disease, as the extent of interaction is unpredictable and dose adjustments may be required.

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ART 2003/2004: The Horizon and Beyond

This overview focuses on drugs already well advanced in development. In view of the large number of substances currently being tested, it does not claim to be complete. Some products are about to be licensed and have been available through expanded access programs. At least four are likely to be approved within the next one to two years: d4T XR, emtricitabine, fos-

amprenavir, atazanavir. The new entry-inhibitor T-20 has been approved in the US in March 2003.

New nukes

Stavudine (Zerit[®]) will soon be available as **d4T XR** (extended release) in a capsulated once-daily formulation (75 mg and 100 mg). The formulation is stable, does not accumulate and seems to cause less polyneuropathy, possibly due to lower peak levels. In the BMS 099 Study, d4T XR was tested double-blind (in combination with lamivudine and efavirenz) against the standard dose of 2 x 40 mg stavudine daily. At 24 weeks, there were no differences in efficacy (CD4+ cell count, viral load) and safety (Pollard et al. 2002). d4T XR was approved by the FDA on December 31, 2002.

Emtricitabine (Coviracil[®], FTC) is a cytidine analog which was developed by Triangle. It has a very long half-life (once-daily dosing with 200 mg) and biochemically resembles lamivudine. In vitro, it was more effective than lamivudine, but this has not been confirmed in humans (Delehanty et al. 1999). Its advantage over lamivudine is questionable since its efficacy is also completely impaired with the M184V point mutation. Newer data from the FTC-301 Trial might lead to drug approval in 2003 (Saag et al. 2002): In this double-blind, randomized study, emtricitabine and stavudine, both in combination with didanosine and efavirenz, were compared in 571 treatment-naïve patients. The study was stopped after a mean follow-up of 42 weeks. After this period, the probability for virologic failure after one year, estimated by Kaplan-Meier curve, was 14 % in the stavudine group versus 6 % in patients receiving emtricitabine; the study investigators considered the difference great enough to prematurely end the trial. Toxicity was also higher in the stavudine group. In the Montana Study, the good tolerability of a once-daily combination with emtricitabine, didanosine and efavirenz seems to be confirmed (Molina et al. 2001). After the acquisition of Triangle by Gilead, the development of a fixed

combination of emtricitabine and tenofovir in one single tablet is planned.

DAPD (Amdoxovir) is a guanine analog developed by Triangle. DAPD is converted in vivo to the highly potent DXG. It is currently being tested in Phase I/II studies (Corbett et al. 2001). DAPD is effective against zidovudine/lamivudine-resistant viruses, including viruses with an insertion at codon 69, which confers multi-resistance against all nucleoside analogs. Sensitivity seems reduced in the presence of mutations such as K65R and L74V (Chong et al. 2002, Mewshaw et al. 2002). In cell cultures the drug has synergistic effects with the fusion inhibitor T-20, which could be useful in the future (Trembley et al. 2002). Equally pleasing is its good efficacy against hepatitis B viruses. Reports on possible lens anomalies are less satisfying. Although the association with DAPD is not yet certain, the company was immediately required by the FDA to study this issue further before continuation of trials.

A look into the lab – Experiments in cell cultures have shown that **DPC 817**, a new oral cytidine analog from BMS with a long half-life, is very effective in the presence of zidovudine/lamivudine resistance mutations (Schinazi et al. 2002). The same appears to be true for **ACH-126,443** (Beta-L-Fd4C), an enantiomer of DPC 817, developed by Achillion Pharmaceuticals. It would appear to allow once-daily dosing and also to be effective against multi-resistant HIV strains and against hepatitis B viruses. Phase IB studies in HIV infected patients are being performed for both drugs. There was similar news of **BCH-13520**, a drug by Shire BioChem Inc. In this case, however, first reports of resistance mutations (Q15M and the insertion at codon 69) have been published (Bethell et al. 2002). **MIV-301 (Alovudine, FLT)** is a thymidine analog, which was initially tested in the 80s but abandoned at the time, mainly due to myelotoxicity. MIV-301 could be celebrating a comeback, as it seems to have excellent efficacy against nuke-resistant viruses (Kim et al. 2001).

Out of sight, out of mind: The following drugs are currently not being pursued, as they are either too toxic or have poor efficacy:

Adefovir dipivoxil (bis POM PMEA)	from Gilead Sciences
dOTC (BCH-10652)	from BioChem Pharma
FddA (Beta-fluoro-ddA, Lodenosine [®])	from US Bioscience
Lobucavir	from BMS

New NNRTIs

Even more than with any other drug class, the industry has the following motto: If one cannot come up with a new drug that is at least effective against efavirenz- and nevirapine-resistant viruses, one might as well not continue with the research. “Me-too” drugs are not needed. In the meantime various drugs have already been abandoned; the road to approval is especially long and hard for NNRTIs, even though they are relatively cheap to develop. Many of the drugs featured below will therefore not reach market development.

TMC 125 is a new second generation NNRTI. It is effective against both wild-type viruses and viruses with almost all of the classical NNRTI mutations (such as K103N, Y181C). In a Phase IIB study, in which 16 patients on stable ART mostly with several NNRTI mutations were treated with 900 mg TMC 125 BID for 7 days, the viral load dropped by a median 0.9 log, and in some cases up to 1.7 log (Gazzard et al. 2002, Sankatsing et al. 2002). Even after this timepoint, viral load continued to decrease. TMC 125 was well tolerated. The half-life is long, and the drug is metabolized in the liver. Although first pharmacokinetic data indicates unfavorable interactions with PIs (especially indinavir and saquinavir), TMC 125 appears to be developing into a strong and promising drug, with a high genetic barrier.

DPC 083 is a second generation NNRTI, which is also said to be effective against NNRTI-resistant viruses. In a Phase II study, in which the drug was tested in two doses of 100 and 200

mg qd in patients with NNRTI treatment failure (viral load > 1000 copies/ml), 4/10 patients who, based on the resistance profile, received DPC 083 as the only effective drug, achieved a viral load of < 400 copies/ml (Ruiz et al. 2002). However, the data from this study was unsatisfactory. There was no data on resistance mutations in these patients, and no clear dose effect with regard to both effectiveness and side effects. In a previous “early” Phase III study, which had compared three different doses of DPC 083 double-blind (50 mg, 100 mg, 200 mg) in some 100 treatment-naïve patients, the effect against wild-type viruses was comparable to that of efavirenz. The side effects seemed to be less.

GW420867X is a quinoxaline-NNRTI from GlaxoSmithKline, which has been shown to be quite effective in vivo in combination with zidovudine and lamivudine (Arasteh et al. 2001). It has good CNS penetration and would probably be a candidate for once-daily dosing (Thomas et al. 2000). As monotherapy, GW420867X decreased viral load by 1.5 log after 8 days, and there were no differences among the various doses investigated (50 mg, 100 mg, 200 mg). The side effects – neurological, gastrointestinal, hepatic – resemble the typical NNRTI complaints; rash was uncommon. However, cross-resistance seems to exist to nevirapine and efavirenz, and it is to be expected that development will be stopped.

Capravirine (AG1549, previously S-1153) is a relatively well-advanced NNRTI, which was initially developed by Shionogi Pharmaceuticals (Fujiwara et al. 1998) and subsequently sold to Agouron. Capravirine is effective in vivo even against viruses with the K103N mutation (Wolfe et al. 2001) and was therefore a hopeful candidate in the battle against NNRTI-resistant viruses. After animal studies in dogs showed an unusually high rate of vasculitis after higher doses, Agouron stopped all Phase II/III clinical trials last year. Safety evaluations have now shown that capravirine does not cause such side effects in humans (Hawley et al. 2002), and in the meantime development will continue. The dose will probably be set at 2 x 700 mg/day.

Emivirine (EMV, MKC-442, Coactinon) is an NNRTI which requires twice-daily dosing and has good tolerability (Szczzech et al. 2000). The main side effects are nausea and the efavirenz-typical dizziness. In a study of patients with relatively low treatment experience, efficacy was good; 82 % of patients had a viral load below 400 copies/ml at 16 weeks, on a combination of stavudine, didanosine and emivirine (Johnson et al. 1999). Unfortunately, the drug seems to be a “me-too” product. There are no differences when compared to the other NNRTIs, and significant cross-resistance (Jeffrey et al. 1999, McCreedy et al. 1999) and PI-interactions (Blum et al. 1998) exist. Further development seems uncertain; the FDA has deemed the available data insufficient for approval.

Out of sight, out of mind - The following NNRTIs are currently not being pursued, as they are either too toxic or have poor efficacy:

Calanolide A	from Sarawak MediChem Pharmaceuticals
Ateviridine	from Upjohn
Loviride	from Janssen Pharmaceuticals
HBV-097	from Hoechst-Bayer
PNU142721	from Pharmacia & Upjohn

New protease inhibitors (PIs)

Fos-amprenavir (GW433908) is a calcium phosphate-ester of amprenavir with better solubility and resorption than the parent compound. It is generally well tolerated, and patients would have to take either 2 x 1 or 1 x 2 pills daily when fos-amprenavir is boosted with ritonavir. This compares favorably with the unacceptable 8 pills bid of standard amprenavir dosage.

In the NEAT Study (APV30001), fos-amprenavir is currently being compared with nelfinavir in treatment-naïve patients (Rodriguez et al. 2002). 251 patients were randomized open-label to fos-amprenavir or nelfinavir, with a nuke backbone of

lamivudine and abacavir. Preliminary 24-week data shows that 54 % versus 40 % of patients (ITT) reached an undetectable viral load. The difference in efficacy was more pronounced in patients with a high viral load. There was also less diarrhea in the fos-amprenavir group. As a potent inductor of amprenavir metabolism, efavirenz can significantly lower plasma levels. This does not happen when fos-amprenavir is boosted with ritonavir, as a study recently demonstrated (Wire et al. 2002): 32 healthy volunteers received one dose of fos-amprenavir with either 100 mg ritonavir bid, 100 mg ritonavir bid plus efavirenz, or 200 mg ritonavir bid plus efavirenz. Overall, the outcomes were similar. In brief: efavirenz does not change anything if ritonavir is given in addition to fos-amprenavir. Even 100 mg ritonavir significantly influences plasma levels; 200 mg neither cause more side effects nor achieve further increases in plasma levels, although lipid levels may increase slightly.

Atazanavir (Reyataz[®]) is a once-daily PI with a favorable lipid profile (Robinson et al. 2000) and an antiviral potency which seems comparable to that of nelfinavir (Squires et al. 2001, Cahn et al. 2001). The 400 mg dose is currently being tested in phase III studies (Pillero et al. 2002). Recently, data from a large study comparing atazanavir with efavirenz (with AZT+3TC as the nuke backbone) was presented (Squires et al. 2002). There were no differences with regard to virological response. However, the proportion of patients with < 50 copies/ml was very low in both groups, which is likely to be a methodological problem in this (probably too large) trial. Lipid levels were clearly better in the atazanavir than in the efavirenz group. The primary resistance-conferring mutation for this drug seems to be 150L; this mutation does not interfere with sensitivity to other PIs (including amprenavir) and may possibly even improve it. Interestingly, amprenavir selects for another mutation exactly at this codon – 150V; the drug thus seems to select on a different basis than amprenavir (Colonno et al. 2002).

Based on the available data, atazanavir could become a good option for initial therapy. The drug is already available in an

expanded access program and will probably be approved in 2003.

Increases in bilirubin levels seem to be a frequent problem. The mechanism for this resembles that of the Gilbert syndrome (and the increased levels with indinavir); there are increased levels of indirect bilirubin due to reduced conjugation in the liver. Although to date no serious hepatic disorders have been described, liver function should be monitored.

Studies of drug interactions in healthy volunteers have shown that rifabutin does not significantly influence atazanavir levels. In contrast, efavirenz may lower plasma levels due to enzyme induction, probably through induction of CYP3A4 (Preston et al. 2002). Concomitant therapy with efavirenz will therefore require an increased dose of atazanavir. Adding 200 mg of ritonavir when giving efavirenz can diminish this effect, presumably also counteracting any favorable effects on lipid levels.

Tipranavir is the first non-peptide protease inhibitor and shows good efficacy against PI-resistant viruses (Larder et al. 2000). In a study of 41 patients previously treated with at least two PIs, tipranavir still showed efficacy in 35 patients (Schwartz et al. 2002). Only the combination of the V82T and L33 point mutations led to a reduction in sensitivity. Oral bioavailability of tipranavir is not very good, and it always requires ritonavir boosting (inhibition of the CYP3A4 system), as a trial in 113 HIV negative volunteers has shown. Ritonavir increases C_{max} at least 4-fold and C_{min} at least 20-fold.

Mozenavir (DMP-450) is a cyclic PI with good solubility, which was initially developed by Dupont and has now been sold to Triangle. The required dose will probably enable manufacture of a single pill (Sierra-Madero 2001). A disadvantage of the drug is its short half-life. As with indinavir, three daily doses will probably be necessary; the resistance profile is also similar. In a small Phase I/II study in 50 patients, virological efficacy was comparable to indinavir. Fortunately, the longer QT-intervals, which had occurred in dogs, were not observed.

Numerous other PIs are already in early clinical trials. Examples include the drugs TMC 114 and TMC 126 from Tibotec, which should be effective especially against PI-resistant viruses. First Phase II trials are ongoing.

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Entry inhibitors

There are three crucial steps for entry of HIV into the CD4+ T cell:

- binding of HIV to the CD4 receptor (“attachment” – target of attachment inhibitors),
- binding to co-receptors (target of co-receptor antagonists), and finally
- fusion of virus and cell (target of fusion inhibitors).

All three drug classes are currently summarized as entry inhibitors. Even if the antiviral effects of the drugs now being tested are not overwhelming, the availability of new drugs with different mechanisms of action could open up new possibilities for the treatment of HIV infection.

Attachment inhibitors

BMS-806 is an “early” attachment inhibitor, which, independently of co-receptors, binds to HIV gp120 specifically and reversibly, and so prevents the attachment of HIV to CD4+ T-lymphocytes (Lin et al. 2002). It has oral bioavailability with low plasma protein binding and could probably be taken in

tablet form. Animal studies have shown good tolerability. There is hope that there might be an additive, perhaps even synergistic effect with other entry inhibitors. Enthusiasm about this drug have been slightly dampened by the demonstration that different HIV isolates have shown differences in sensitivity to BMS 806, indicating potential rapid development of resistance.

Pro-542 is a soluble antibody-like fusion protein, which also prevents attachment of HIV to CD4+ T-lymphocytes by binding to gp120. Phase I studies have shown good tolerability, and viral load decreased even after a single infusion (Jacobson et al. 2000). Pro-542 has already been tested in children (Shearer et al. 2000). In the SCID mouse model, Pro-542 has shown remarkable efficacy (Franti et al. 2002). However, the impractical route of administration (infusion) must be improved.

Co-receptor antagonists

SCH-C is a CCR5-receptor antagonist with oral bioavailability and a potent in vitro activity against numerous HIV isolates (Strizki et al. 2001). In healthy volunteers, side effects such as arrhythmias (longer QT-interval) occurred mainly at higher doses. This problem appears to be absent with low dosage, and the FDA has given the go-ahead for further development. A pilot study in 12 HIV patients, who received SCH-C for 10 days (the dose was significantly reduced to 2 x 25 mg/daily) showed that all 10 patients had a decrease in viral load of more than 0.5 log, and 4 patients of more than 1.0 log (Reynes et al. 2002). This effect persisted even a few days after completion of therapy. However, viral escape mutants have already been described for SCH-C, which are cross-resistant to other CCR5-receptor antagonists (Riley et al. 2002, Xu et al. 2002). **SCH-D** is claimed to be more potent and better tolerated than SCH-C, and therefore seems to have better chances for further development (Chen et al. 2002). However, first reports have described development of resistance, probably via changes in the HIV *env* gene.

Pro-140 is a CCR5-antagonist, which acts as a monoclonal antibody (Trkola et al. 2001). In animal studies (SCID mouse model), single doses of the drug achieved significant and dose-related reductions in viral load. (Franti et al. 2002). Clinical data is still lacking, and there is no information on tolerability.

AMD-3100 is a CXCR4-receptor antagonist as is **T-22**. Results to date could be described as discouraging. In a complicated study with 12 patients, who received a continuous infusion over 10 days, no reduction of viral load occurred. In addition, a variety of side effects such as thrombocytopenia, orthostasis and arrhythmias were experienced (Hendrix et al. 2002). However, AMD-3100 appears to be effective against CXCR4-receptor-tropic viruses (Schols et al. 2002, van Rij et al. 2002). The one patient who exclusively harbored such a virus population was the only one to show a decrease in viral load by 0.87 log after 11 days, and 1.34 log after 18 days. Resistance mutations have been described both for AMD-3100 and T-22. Whether development of AMD-3100 will be pursued is uncertain. Follow-on drugs, possibly for oral administration, are apparently being studied.

Fusion inhibitors

T-20 (Enfuvirtide, Fuzeon®): Hardly a day goes by without mention of T-20 in the media, and every other patient asks him- or herself and the physician, why he or she is not yet receiving the “new drug”. T-20 is the prototype of fusion inhibitors. It is a relatively large peptide, comprised of 36 amino acids, and must therefore be given by subcutaneous injection like insulin. It binds to an intermediate structure of the HIV gp41-protein, which appears during entry of HIV into the target cell, i.e. during fusion.

In one of the first studies with T-20, HIV patients were given different doses intravenously as monotherapy. There was a dose-related effect, and with the higher dose of 2 x 100 mg per day, median viral load was reduced by almost 2 log (Kilby et al. 1998). Because of the impracticability of twice-daily infusion,

the first study using subcutaneous application was initiated shortly afterwards. 78 highly treatment-experienced patients received T-20 in addition to stable HAART – either via an insulin pump or twice-daily subcutaneously (Kilby et al. 2002). Again, positive dose-related effects on viral load were shown in both groups. However, maximal suppression was lower than with infusions, and the maximum decrease was 1.6 log. More importantly, the effect was short-lived; after 28 days, in most cases viral load had returned to baseline levels. The main side effects in this study were reactions (mostly mild) at the injection site.

Long-term evaluations have shown that the drug is also well tolerated over longer periods of time (Lalezari et al. 2000). In the T20-205 Study, 70 patients, mostly PI-experienced, received 2 x 50 mg T-20 subcutaneously daily for 48 weeks. Only few patients discontinued treatment prematurely due to side effects. After 48 weeks, a constant effect on viral load was still evident in at least one third of patients, but it became evident that T-20 was of more benefit to patients who received other new drugs for HAART at initiation of T-20. In the first Phase II study (T20-206) for which 48-week data is available, the strategy was therefore changed: 71 NNRTI-naïve patients received different doses of T-20 in addition to a new ART regimen (Lalezari et al. 2002). In this study, the additional effect of T-20 was weaker, but still present, although the study was not intended to show differences between the individual groups. Nevertheless, this study demonstrated that the simple addition of T-20 to an otherwise unchanged treatment regimen would not be that beneficial. Approximately two thirds of the T-20 patients in this study had local reactions (mostly mild) at the injection site. T-20 was generally well tolerated.

The preliminary and actually unexpected good data from the first Phase III studies led to considerable media attention for T-20 during the summer of 2002 (Henry et al. 2002, Clotet et al. 2002). TORO 1 (“T-20 versus optimized regimen only”, previously T20-301 Study) enrolled 491 patients in North America

and Brazil. Patients were randomized 2:1 to receive 2 x 90 mg T-20 subcutaneously or not, on an optimized HAART regimen (Henry et al. 2002). Almost all patients were heavily pre-treated and harbored multiresistant viruses at entry. Again, the results were astounding: The addition of T-20 clearly reduced viral load compared to the optimized therapy “only”. At 24 weeks, the reduction of viral load was 1.70 log in the T-20 group, compared to 0.76 log in the controls – a surprising difference of 0.93 log. In TORO 2 (T20-302), the same design was tested in 504 patients in Europe and Australia (Clotet et al. 2002). The difference at 24 weeks was 1.43 versus 0.65 log – still a difference of 0.78 log.

Summary, evaluation and prospects of T-20: Patients with a well-controlled viral load or who still have options with “classical” HAART would probably not require T-20 immediately. For salvage therapy, however, the drug seems to be quite useful. It must be stressed, however, that even in this setting wonders cannot be achieved, the antiviral effect after one year being just about one log. Although there is still no data from studies with clinical endpoints, patients who currently have no other treatment options might benefit clinically from this drug.

T-20 has been approved in the US in March 2003. The drug will presumably not be available for all patients immediately, as there are considerable logistical problems that still need to be solved in manufacturing. According to Roche, this is one of the most complicated drugs that the company has ever manufactured: 106 steps are necessary for synthesis. This will presumably translate into high product pricing; one can thus expect that the cost of a T-20-containing HAART regimen will be double that of one without.

T-20 is certainly not as sensational as it has been portrayed over the last 12 months. From a medical point of view, it is a major breakthrough that this mechanism of action for inhibiting viral replication actually works. A combination of different entry inhibitors, which would hopefully act synergistically, both with

each other and with HAART, will likely inhibit HIV replication more efficiently than traditional HAART.

T-1249 is the second fusion inhibitor to be developed and is possibly more promising than T-20. T-1249 is a peptide that binds to the hairpin-structure of the HIV envelope protein gp41 and consequently prevents fusion of the viral and host cell membranes. The drug has favorable pharmacokinetics with a once-daily dose as well as activity against T-20-resistant viruses (Lambert et al. 1999). So far data is available from a Phase I/II study (Eron et al. 2001, Gulick et al. 2002). 72 heavily pre-treated HIV patients received T-1249 as monotherapy subcutaneously for 14 days, in doses ranging from 6.25 mg to 50 mg per day (as a once- or twice-daily dose). A dose-related reduction of viral load was observed (maximum reduction – 1.4 log with the 50 mg dose), with the plateau not yet reached. 40 % of patients experienced a local reaction at the injection site; one patient developed grade 4 neutropenia. Whether the one patient who acquired a rash with fever had a hypersensitivity reaction is still unclear. Selection of T-1249-resistant isolates is possible in vitro.

Integrase inhibitors

The integrase is one of the three key enzymes encoded by the HIV *pol* gene. This enzyme is involved in integration of viral DNA into the host genome (Nair 2002). Integrase inhibitors differ from entry inhibitors as they do not prevent entry of the virus into the cell. Although human cells probably do not have an integrase, the development of new and effective drugs in this class is proving difficult, and progress is slow (Debyser et al. 2002). A good number of drugs have appeared over the last years, only to disappear again just as quickly.

S-1360, which was developed by Shionogi/Glaxo, shows initial promising data (Yoshinaga et al. 2002). In vitro (using an MTT assay), S-1360 is effective against a variety of isolates, including all NRTI- and PI-resistant mutants. There seems to be synergy with zidovudine, lamivudine, nevirapine and nelfinavir. In

animal studies (mice, rats, dogs), the drug has so far shown little toxicity. The molecule is small, so that oral dosing is likely to be possible. The drug was well tolerated in healthy volunteers (Fujiwara 2002).

Merck has also been working on integrase inhibitors. After some difficulties, the first prototypes are now ready for testing in clinical trials (Hazuda 2002). A new class, the naphthyridine-7-carboxamides, shows good oral bioavailability. L-870812 and L-870810 are currently the most promising drugs in this class. In an animal model in SIV-infected monkeys, viral load decreased in 4 of 6 animals by more than one log. Phase I trials were started based on this data.

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Immunotherapy and its Relevance in Practice

In recent years, in addition to “conventional” ART, immunological treatment strategies have been investigated to an increasing extent (reviews in: Mitsuyasu 2002, Sereti et al. 2001). Increasing numbers of studies are being published on approaches with interleukin-2 or hydroxyurea. All of these therapies still lack proof of clinical benefit. Some important approaches are nevertheless addressed briefly below.

Interleukin-2

Interleukin-2 (IL-2, aldesleukin, Proleukin[®]) is a cytokine that is produced by activated T cells and leads to proliferation and cytokine production by T cells, B cells and NK cells (review in: Paredes et al. 2002). It has been employed in oncology for years. IL-2 was already used in the early nineties, either intravenously or as a continuous infusion in HIV infected patients (Wood et al. 1993). It is now usually administered subcutaneously.

The most important effect of IL-2 in HIV medicine is the rise in CD4⁺ and CD8⁺ T cells, which in individual cases may be quite impressive (Kovacs et al. 1996). Several randomized studies have consistently demonstrated significant increases in CD4⁺ T cells. After administration of IL-2, CD45RO⁺ memory cells initially increase, followed by naive CD45RA⁺ T cells. The life span of CD4⁺ and CD8⁺ T cells may also be increased.

IL-2 is usually given in doses of 2 x 4.5 million I.E. subcutaneously over 5 days, in cycles 6-8 weeks apart (Davey et al. 2000, Losso et al. 2000, Abrams et al. 2002, Lelezari et al. 2000, Hengge et al. 1998). Daily treatment with a low dose has also been investigated (review in: Smith 2001). After 24 to 48 weeks, increases in CD4⁺ cell count were 100-250 cells higher in the IL-2 group than in the controls. Viral load was usually unaffected by IL-2.

Unfortunately, the activation of T cells had no influence on viral reservoirs. Although the initial hope was that IL-2 could be

used to purge virus in the reservoirs and thereby “wash out” latently infected cells from the body, (Chun et al. 1999), it is now clear that this does not occur. In the German COSMIC Study, 56 patients with more than 350 CD4+ T cells/ μ l on HAART were randomized to receive IL-2 or placebo. Although IL-2 led to a normalization of CD4+ cell count in significantly more patients, IL-2 did not influence viral replication, proviral DNA nor latently infected cells (Stellbrink et al. 1998, Stellbrink et al. 2002).

In all larger studies, the combination of IL-2 with HAART has so far demonstrated to be relatively safe. Nevertheless: the drug has considerable side effects; fever, chills and sometimes severe flu-like symptoms with myalgias are usually dose-limiting. The side effects are the result of the IL-2-induced release of cytokines and invariably resolve 2-3 days after the last dose. Paracetamol, rest and intake of electrolyte-rich solutions may be helpful. The side effects, which are more severe than with interferon, cannot be suppressed completely. Some researchers question the rationale of IL-2 treatment, arguing that it might just be the practice of lab cosmetics (“T cells ok, patient sick”). In addition, doubts have been expressed with regard to the quality of the immune response. Are the CD4+ T cells generated by IL-2 of the same quality as “normal” CD4+ T lymphocytes, and – more importantly – do the increases really prevent AIDS? Do patients really have clinical benefit from these difficult IL-2 treatments? Little is also known about the long-term use of IL-2 – the longest study performed to date lasted three years (Gougeon et al. 2001).

Answers to these questions were expected from ESPRIT and SILCAAT, the two ongoing multinational studies. Both were intended to clarify over several years whether IL-2 has bona fide clinical benefits. ESPRIT (<http://www.espritstudy.org>) is a randomized study in which around 4,000 patients with at least 300 CD4+ T cells/ μ l are being treated. SILCAAT (<http://www.silcaat.com>) enrolled patients with 50-299 CD4+ T cells/ μ l and a viral load of < 10,000 copies/ml. 2,000 patients

were to be observed, initially for four years. After enrolment of 1,957 patients in 137 centers in 11 countries, the study was unfortunately stopped in October 2002, although the results of SILCAAT (patients with low CD4+ cells!) would have been of great importance for physicians and patients. The decision to halt the study was probably a business decision: SILCAAT was becoming too expensive for the manufacturer Chiron. While the company is now trying to license the product with currently available data (which might prove difficult), the scientific committee under the leadership of Clifford Lane opposed the discontinuation of the trial. Attempts are currently being made to redirect the study into an academic investigation, so that data from this important trial will not be lost.

The NIH-sponsored ESPRIT study will continue for the time being.

All in all, IL-2 must still be viewed skeptically based on the available data. In our opinion, only a few patients potentially qualify for therapy with IL-2. These are patients with no immunological response, patients whose CD4+ counts remain below 100/ μ l despite good viral suppression over longer periods of time.

Hydroxyurea (Litalir[®])

Hydroxyurea is an old chemotherapeutic agent with relatively low toxicity, which is still being used today in hematology (mostly in chronic myelogenous leukemia). It inhibits DNA synthesis via the ribonucleotide reductase, and leads to an intracellular shortage of deoxynucleotide triphosphates. A synergistic effect on HIV replication in combination with didanosine was demonstrated in 1994.

A randomized, double-blind study from Switzerland attracted attention in 1998 (Rutschmann et al. 1998). The investigators had treated 144 patients with hydroxyurea or placebo in addition to d4T+ddI. After 12 weeks, 54 % of hydroxyurea-treated patients demonstrated a viral load below 200 copies/ml compared to 28 % in the placebo group. Was this the discovery of a

new, cheaper option for HIV treatment? In the light of these seemingly exciting results, the fact that the CD4+ T cell increase in the hydroxyurea group was only 28 versus 107 cells/ μ l in the placebo group had to be tolerated. Hydroxyurea was even more in fashion after publication of the “Berlin-Patient”: a patient, who had been treated with hydroxyurea in addition to indinavir and didanosine during acute infection, had stopped all therapy after a few months and subsequently showed no detectable plasma viremia (Liszewicz et al. 1999). Was this unexpected outcome due to hydroxyurea? Several smaller studies from the US and Argentina seemed to confirm these positive results, seen primarily in combination with didanosine (Hellinger et al. 2000, Lori et al. 1999, Rodriguez et al. 2000). Many treating physicians added the drug to ART, and even children received hydroxyurea. Many already dreamed of a cheap combination of ddI+HU for Africa.

These initial hopes subsided quite rapidly. Although the drug is usually well tolerated, the combination with didanosine and stavudine in particular seemed problematic. Data from early 2000 reported an additive effect, with a frequency of polyneuropathy of almost 30/100 patient years (Moore et al. 2000). The ACTG 5025 Study (Havlir et al. 2001), in which hydroxyurea was evaluated as a “stabilizer” of successful therapy (stable undetectable viral load), led to the temporary demise of this drug in HIV therapy. Three deaths on the combination of ddI+d4T (+IDV) due to pancreatitis, all in the hydroxyurea group, were reported. There was also a higher rate of treatment failure in patients receiving hydroxyurea, probably due to toxicity rather than to virological failure. The risk of pancreatitis on didanosine seems to be four times higher in combination with hydroxyurea (Moore et al. 2001). Randomized studies also failed to show an effect in primary infection: obviously, further Berlin-patients cannot simply be “reproduced”, at least not for hydroxyurea (Zala et al. 2002).

In October 1999, BMS received a warning from the FDA for having too enthusiastically promoted hydroxyurea for HIV

therapy (<http://hiv.net/link.php?id=164>). We think that hydroxyurea should not be used outside clinical trials.

Interferon

The antiretroviral effect of interferon has been known for years (Milvan 1996). The effect of 3 million I.E. daily s.c. is ca. 0.5-1 log (Haas et al. 2000). Higher dosing may pronounce the effect further (Hatzakis et al. 2001). The antiviral effect of interferon was initially not investigated in more depth because of the subcutaneous delivery route and its side effects. There have recently been indications that the drug may be useful for salvage therapy. Pegylated interferons now allow for weekly administration, and improved efficacy with the pegylated drug is anticipated in analogy to the studies in the setting of hepatitis C infection. Schering-Plough is currently involved in trying to license the product. However, there have been setbacks, as with IL-2, and a pivotal multinational study in highly treatment-experienced patients was aborted in October 2002 due to insufficient recruitment.

Other immunotherapies

The prototype of therapeutic vaccination already suffered disaster years ago. **Remune[®]**, a therapeutic vaccine comprised of an envelope-depleted (gp120) virus, which was developed by a team headed by Jonas Salk, although indeed immunogenic, does not seem to provide any clinical benefit (i.e., prolongation of life and delay of disease progression). A large trial was interrupted prematurely in May 1999 as no benefit had been demonstrated for study participants. More than 2500 patients had taken part for a mean of 89 weeks in this multinational study, which was designed to evaluate the addition of Remune[®] to HAART. In addition to the lack of clinical benefit not even advantages with respect to CD4⁺ cell count or viral load could be shown (Kahn et al. 2000). The product is now probably obsolete, even though there have been dubious reports, mainly from Thailand, claiming that some effect exists.

G-CSF and **GM-CSF** have frequently been used in HIV patients. G-CSF (granulocyte colony-stimulating factor or filgrastim) significantly reduces bacterial infections in HIV patients with neutropenia (Kuritzkes et al. 1998). G-CSF also significantly improved survival in patients with CMV retinitis, although the mechanisms were unclear (Davidson 2002). No effect on HIV viral load could be shown. GM-CSF (granulocyte-macrophage colony-stimulation factor or sargramostim) showed a slight effect on viral load in two double-blind randomized studies (Skowron et al. 1999, Brites et al. 2000). However, such approaches cannot be recommended outside of clinical studies. Whether any clinical benefit exists remains unclear.

Cyclosporine A (Sandimmune®) – Immune activation may lead to increased HIV replication, and an attractive treatment hypothesis has been to suppress the immune system in an attempt to slow down viral replication. This is the rationale behind studies investigating the use of cyclosporine A. The drug is normally used for prophylaxis of transplant rejection after allogenic organ transplantation. Between 1997 and 1999, 28 HIV patients were recruited to receive cyclosporine A 4 mg/kg or placebo daily for 12 weeks, with or without antiretroviral therapy (two nucleoside analogs; Calabrese et al. 2002). The results are easily summarized: cyclosporine A had no effect on CD4+ or CD8+ count, nor on expression of activation markers such as CD38 or HLA-DR. Cyclosporine A therefore probably has no future in the therapy of chronically infected HIV patients. Whether, and how, cyclosporine A might improve treatment of acute HIV infection needs to be clarified in further studies. Use of both immunosuppressants (CsA) and immunostimulants (IL-2) in this setting shows the clear discrepancy between scientific knowledge and hope.

Mycophenol (Cellcept®) follows a concept similar to that of hydroxyurea and cyclosporine A. Mycophenol inhibits the inosine monophosphate (IMP) dehydrogenase and is normally used for prophylaxis of acute transplant rejection in patients with allogeneic kidney, heart or liver transplantations, as well as

for some autoimmune diseases. Inhibition of lymphocyte proliferation and reduction of target cells should theoretically inhibit replication of HIV. First reports from small cohorts of patients seem to demonstrate an effect on viral load in some cases (Margolis et al. 2002, Press et al. 2002). Whether this will be confirmed by randomized trials seems uncertain.

Cannabinoids have no effect. A neatly designed study, in which patients could either smoke marijuana or receive TCH (dronabinol, Marinol®) or placebo in addition to HAART, showed no effects on lymphocyte subpopulations or lymphocyte function after three weeks (Bredt et al. 2002).

Interleukin-12 – IL-12 stimulates T lymphocytes and NK cells to generate a Th1-type immune response. In a randomized Phase I study with rhIL-12 100 ng/kg 2 x/week, the drug was well tolerated but had no effect on lymphocyte subpopulations, antigen-specific immune response or viral load (Jacobson et al. 2002). Further development is therefore uncertain. The same would appear to be true for **interleukin-10** (Angel et al. 2000).

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3. Goals and Principles of Therapy

Christian Hoffmann

In the flood of monthly evaluations - including CD4+ count, viral load, routine laboratory, genotypic and phenotypic resistance testing, and drug plasma levels - the ultimate goal of antiretroviral therapy should always be borne in mind:

*To prolong the patient's life,
while maintaining the best possible quality
of health and life.*

This paradigm suggests that not only opportunistic infections and malignancies, but also side effects of therapy, should be prevented. Ideally, antiretroviral treatment should have little or no influence on daily life. Even if a high CD4+ count and a low viral load are useful therapeutic goals, the patient's condition is at least as significant as such laboratory results! Patients, too, often lose focus on what really matters. The response to the doctor's query: "How are you?" is often accompanied by a glance toward the CD4+ count result on the chart: "That's what I'd like to know from you!". It may therefore indeed be useful to reflect upon – alone or with the patient – what one realistically wants to achieve.

Success and Failure of Treatment

Both success and failure of treatment can be evaluated with differing criteria – virological, immunological or clinical. Of these, the earliest indicator is **virological** success or failure (decrease or increase in viral load). This is followed, often a little later, by **immunological** treatment success or failure (rise or fall in CD4+ cell count). **Clinical** treatment failure usually becomes apparent only much later – first the lab values deteriorate, then

the patient! On the other hand, success of treatment may be seen much earlier; many patients suffering from constitutional symptoms rapidly improve on HAART. In the Swiss Cohort, the incidence of opportunistic infections after only three months on HAART was reduced from 15.1 to 7.7 per 100 patient years (Ledergerber et al. 1999). For clinical treatment success, in particular in the prevention of AIDS, immunological success is probably at least as important as virological success (Grabar et al. 2000, Piketty et al. 2001).

Virological treatment success and failure

Virological treatment success is usually understood as a viral load decrease to below the level of detection of 50 copies/ml. This is based on the understanding that, the more rapid and complete the decrease in viral load, the longer the therapeutic effect (Kempf et al. 1998, Powderly et al. 1999, Raboud et al. 1998). In the INCAS Trial, the relative risk for treatment failure (defined here as an increase to $> 5,000$ copies/ml) in patients who had reached a viral load < 20 copies/ml was 20 times lower than in those who had never reached a level below 400 copies/ml (Raboud et al. 1998). On HAART, viral load declines in two phases (see also the chapter on "Monitoring"); there is an initial very rapid decrease in the first weeks, followed by a slower phase, in which plasma viremia is reduced only slowly. A decrease to below the level of detection should be reached by 3-4 months; in cases of very high baseline viral load this may take 4 or 5 months. A viral load above the level of detection after 6 months of treatment is generally seen as failure. The same is true if a rebound in viral load is confirmed by a second determination after a short interval. In such cases, improvements in therapy (e.g. compliance, change in the regimen) should soon be considered.

The cut-off point of 50 copies/ml is arbitrary. It is based on the currently available assays for measurement of viral load. Whether 60 copies/ml are indeed worse than 30 copies/ml and indicate a lesser success of treatment has not yet been proven. At

these low levels, methodological inaccuracies must be taken into account. A single viral load rebound ("blip") to low levels (up to 1000 copies/ml) is often irrelevant (see below).

A viral load "below the level of detection" of 50 copies/ml means just that – no more, no less. Numerous studies indicate that replication and therefore development of resistance can continue even with an undetectable virus load. 50 viral copies/ml indicate that 5 liters of blood contain 250,000 viruses; in addition, even more actively replicating viruses are present in the lymphatic organs. Thus, theoretically, measurable viremia, even at very low levels, may possibly translate to a higher risk of resistance in the long-term. Perhaps there is indeed a relevant difference between 100 and 10 copies/ml with regard to risk for developing resistance. But we just don't know yet.

The good news: Morbidity and mortality may be lowered even if the viral load is not decreased below the level of detection (Mezzaroma et al. 1999, Deeks et al. 2000, Grabar et al. 2000). This should be borne in mind when treating patients who have only a limited number of treatment options. In such cases, it may be useful to abandon viral load as a measure for success. In patients with multiresistant viruses, virological success may not be possible; here, stabilizing the CD4+ count should be of top priority. Patients often remain immunologically stable for relatively long periods of time, even with insufficient viral suppression.

The most important risk factors for virological treatment failure are extensive pre-treatment with antiretroviral drugs (pre-existing resistance mutations) and non-compliance (review: Deeks et al. 2000). Whether viral load and CD4+ count at baseline really play a role has not yet been proven conclusively; in several cohorts no influence was detected (Cozzi Lepri et al. 2001, Phillips et al. 2001, Le Moing et al. 2002; see also the chapter "When to start HAART".)

How long does virological treatment success last?

Little is known about how long treatments remain effective. Following the six years during which HAART has been employed, a surprisingly high number of adequately treated patients still have viral loads below the level of detection, even after this time span. One of the few trials with a longer follow-up period studied 336 antiretroviral-naïve patients who had reached a viral load below 50 copies/ml within 24 weeks (Phillips et al. 2001). After 3.3 years, the risk of viral rebound was relatively high at 25.3 %. More detailed analysis showed that a large proportion of the patients experiencing viral rebound had actually interrupted HAART. True virological failure was only seen in 14 patients, which corresponds to a risk of 5.2 % after 3.3 years. Most importantly, the risk of virological failure decreased significantly with time. Thus, if treatment is not interrupted, viral load may remain below the level of detection for many years.

"Blips" – Do they mean virological failure?

Blips are transient increases in viral load. They occur in 20-40% of patients and have been shown to be associated with a higher level of viral replication. Blips often worry both patients and clinicians. Strictly speaking, if one defines virological success as < 50 copies/ml, blips signify treatment failure. However, increasing data indicates that blips seem to have no consequences in the medium-term, and do not necessarily indicate immunological or even clinical treatment failure (Havlir et al. 2001, Moore et al. 2002, Sklar et al. 2002). This is true both for patients on first-line therapy and for highly treatment-experienced patients. However, longer follow-up is still required to exclude that patients with occasional blips are at more risk of developing resistance. In at least one recent analysis, the risk for treatment failure after 18 months was approximately doubled (Greub et al. 2002). Following presently available data, blips should not necessitate an immediate change of therapy. They can and should, however, raise the opportunity for a conversa-

tion with the patient on the subject of compliance. It should be noted that viral load may also temporarily increase after immunizations (Kolber et al. 2002).

Immunological treatment failure and success

Immunological treatment success is generally defined as an increase in the CD4+ cell count. A more precise definition for immunological treatment success does not currently exist. Depending on the study, increases *by* 50, 100 or 200 CD4+ T cells/ μ l or increases *to* above 200 or 500 CD4+ T cells/ μ l are defined as success. Failure is usually described as the absence of an increase or decrease in the CD4+ T cell count in patients receiving HAART.

Prediction of a rise in CD4+ count in patients on HAART is difficult as there is significant individual variation. As with the decrease in viral load, the increase in CD4+ count occurs in two phases. After a first, usually rapid increase over the first three to four months, further increases are considerably less pronounced. In a prospective study involving some 1,000 patients, CD4+ count in the first three months increased by a median of 21.2 CD4+ T cells/ μ l per month; in the following months the increase was only 5.5 CD4+ T cells/ μ l (Le Moing et al. 2002). There is inconclusive data as to whether lower CD4+ counts at baseline result in a slower increase. However, normalization of the CD4+ count (> 500 / μ l) appears to be less likely and/or takes longer, if the CD4+ count was low at initiation of therapy (Kaufmann et al. 2002, Valdez et al. 2002). Immunological treatment success is not necessarily linked to maximal viral suppression; even partial suppression may lead to improvement in the CD4+ T cell count (Kaufmann et al. 1998, Mezzaroma et al. 1999). Neither is the level of initial viral load significant; what seems to be crucial is that the viral load remains lower than before treatment (Deeks et al. 2002).

Discordant response

Failure to achieve one or two of the therapeutic goals – clinical, immunological and virological - is referred to as a discordant response. Some patients may have virological treatment success without an immunological improvement, continuing to have a very low CD4+ T cell count despite undetectable viral load (Piketty et al. 1998, Renaud et al. 1999, Gabran et al. 2000, Piketty et al. 2001). Conversely, HAART may be immunologically extremely effective and induce significant increases in the CD4+ count, while the viral load remains detectable. The frequencies of such discordant responses are outlined in the table below.

Table 3.1: Prospective cohort studies, treatment response*

Response to HAART	Piketty et al. n = 150	Grabar et al. n = 2236
Virological and immunological response	60 %	48 %
Discordant: only immunological response	19 %	19 %
Discordant: only virological response	9 %	17 %
No treatment response	12 %	16 %

* Immunological response: rise in CD4+ T cells > 100/μl after 30 months (Piketty et al. 2001) or > 50/μl after 6 months (Grabar et al. 2000). Virological response: continually at least 1 log below baseline or < 500 copies/ml (Piketty et al. 2001) or < 1000 copies/ml (Grabar et al. 2000).

Immunological response is often moderate in comparison to virological response, particularly in older patients. With increasing age, the immune system becomes less capable of regenerating, probably due to thymus degeneration (Lederman et al. 2000). Various studies have demonstrated that the probability of *not* achieving a rise in CD4+ count increases with patient age and with progressive decrease in thymus size as detected by CT (Goetz et al. 2001, Marimoutou et al. 2001, Piketty et al. 2001, Teixeira et al. 2001, Viard et al. 2001).

Practical considerations in dealing with viral load and CD4+ count

- Viral load, since it can be directly affected, is the most important parameter in treatment monitoring.
- If possible, use only one type of assay (in the same lab) – keep in mind that there is considerable methodological variability (up to half a log)!
- Virological success should be monitored one month after initiation or modification of HAART.
- Viral load should be below 50 copies/ml after 3 months (with high initial viral load, after 6 months at the latest) – if it is not, check for the cause!
- The greater the decrease in viral load, the more durable the response to treatment.
- Transient, low-level increases in viral load (blips) are often of no significance – but VL should be remonitored at short intervals (after 2-4 weeks).
- The older the patient, the likelier a discordant response (low viral load with no significant increase in CD4+ count).
- In contrast to viral load, increase in CD4+ T cells, i.e. immunological success, is difficult to influence. CD4+ T cells are probably more predictive of the individual risk for AIDS.
- Once CD4+ count is above 400-500/ μ l, controls can be performed less frequently. Keep in mind that with higher CD4+ counts, values may vary considerably from one measurement to the next (which may cause the patient either a false sense of euphoria or unnecessary concern).

Clinical treatment success and failure

Clinical treatment success is dependent on virological and immunological therapeutic success. In individual patients, clinical response is not always easy to assess. After all, there is no way to show what might have occurred if treatment had not been started. As an asymptomatic patient cannot feel any better, it may be difficult to find good arguments to continue treatment in the presence of side effects, which, at least temporarily, may affect the quality of life.

Clinical success is almost always evaluated via clinical end-points (AIDS-defining illnesses, death), although the improvement on HAART in a patient with considerable constitutional symptoms should also be seen as clinical success. With regard to risk of disease progression, immunological response is at least as important as virological response (Table 3.2).

Table 3.2: Risk of progression, as defined by immunological and virological treatment response. See previous table caption for definitions. 95 % confidence interval in parentheses.

	Grabar et al. 2000	Piketty et al. 2001
CD4+ T cells at baseline (median)	150	73
	Relative risk	Relative risk
Virological and immunological response	1	1
Immunological response only	1.6 (1.0-2.5)	6.5 (1.2-35.8)
Virological response only	2.0 (1.3-3.1)	9.7 (1.6-58.4)
No treatment response	3.4 (2.3-5.0)	51.0 (11.3-229.8)

The degree of virological response is also of great importance. In the Swiss Cohort, 6.6 % of patients with a viral load constantly below the level of detection suffered AIDS or died after 30 months. In contrast, AIDS or death occurred in 9.0 % of patients with viral rebound, and in 20.1 % of those whose viral load never became undetectable (Ledergerber et al. 1999). The importance of a complete and sustained virological treatment response for clinical success has also been reported in other cohorts (Salzberger et al. 1999, Thiebaud et al. 2000).

Clinical failure is usually defined as development of an AIDS-associated condition or death. However, illness is not always indicative of clinical treatment failure. A good example is the immune reconstitution syndrome, where a pre-existing, sub-clinical infection becomes apparent during the first weeks following initiation of antiretroviral therapy. On the other hand, if a patient suffers serious side effects or even dies as a result of them, this should also be seen as treatment failure.

What can be achieved today?

Every HIV clinician sees the remarkable strides made possible by HAART reflected in his or her own patients (Table 3.3). In many areas, the incidence of AIDS has been reduced to less than a tenth (Mocroft et al. 2000). Today, in many Western countries, almost all AIDS cases occur in patients who are not being treated with antiretroviral therapy – usually because they are unaware of their infection. The mortality rate has declined to levels far below that of even a few years ago (Mocroft et al. 2002).

Table 3.3: Patient case (female, 41 years) demonstrating advances in treatment due to HAART*

		CD4+ T cells	Viral load
Feb 95	AZT+ddC	23 (4 %)	NA
Nov 96	AIDS: Toxoplasmosis, MAC, Candida esophagitis	12 (1 %)	815.000
Feb 97	d4T+3TC+SQV	35 (8 %)	500
June 97	stopped HAART due to polyneuropathy		
July 97	AZT+3TC+IDV	17 (4 %)	141.000
Mar 98		147 (22 %)	< 50
Mar 99	AZT+3TC+IDV+NVP	558 (24 %)	100
Mar 00		942 (31 %)	< 50
Mar 02		1132 (33 %)	< 50

* Excellent immune reconstitution despite initially severe immunodeficiency and several AIDS-defining illnesses. All primary/secondary prophylaxes (MAC, Toxoplasmosis, PCP) have now been discontinued.

Data from prospective, controlled studies on this dramatic change is still relatively sparse, there being few randomized trials with clinical endpoints (Hammer et al. 1997, Cameron et al. 1998, Stellbrink et al. 2000). The results seen in these studies, which led to licensing of PIs, were also relatively modest, due their design. In a multi-center trial, 1,090 clinically advanced patients received zidovudine liquid formulation or placebo in addition to their ongoing treatment. Probability of AIDS and death with a follow-up of 29 weeks was 21.9 % in the zidovudine arm and nearly double (37.5 %) in the placebo arm (Cameron et al. 1998). In the SV14604 Study, the largest study of its kind to date, involving 3,485 patients, the frequency of AIDS and death was reduced by about 50 % in the group receiving AZT+ddC+saquinavir hard gel, compared to the groups on dual therapy (Stellbrink et al. 2000).

Due to the success of antiretroviral therapy, the number of clinical endpoints that occur is fortunately now extremely low. As a result, the duration of any contemporary study to prove clinical benefit of one combination over another would have to be very long. Only rarely will such investigations be undertaken in the future (Raffi et al. 2001).

SILCAAT, a large multi-center study that had enrolled around 2,000 patients with less than 300 CD4+ T cells/ μ l was terminated in October 2002 because the number of clinical endpoints reached was too low to enable adequate detection of any differences.

With regard to opportunistic infections and malignancies, the effect of HAART is equally apparent on their clinical course as on their incidence. Illnesses such as cryptosporidiosis or PML can be cured, while Kaposi's sarcoma can resolve completely without specific therapy. Prophylaxis of pneumocystis, toxoplasma, CMV or MAC can usually be safely withdrawn. These effects are discussed in more detail in the corresponding chapters.

Table 3.4: Decline in morbidity and mortality in large cohorts

	Where? (n)	Patients (Period)	Mortality (/100 py)	Morbidity (/100 py)
Palella 1998	USA (1255)	< 100 CD4+ T cells/ μ l (1/94-6/97)	29.4 $\rightarrow$ 8.8	21.9 $\rightarrow$ 3.7*
Ledergerber 1999	Switzerland (2410)	6 months <i>before</i> versus 3 months <i>after</i> HAART (9/95-12/97)	NA	15.1 $\rightarrow$ 7.7
Mocroft 2000	Europe (7331)	All (94-98)	NA	30.7 $\rightarrow$ 2.5
Mocroft 2002	Europe (8556)	All (94-01)	15.6 $\rightarrow$ 2.7	NA

* MAC, PCP, CMV. Mortality/Morbidity each per 100 py = patient years

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Eradication – Is it Feasible?

At this point in time, eradication of HIV in the sense of a cure is unrealistic. Although as late as 1997, many still dreamt of eradication, leading researchers now incline towards pessimism. The problem lies in the pool of latently infected CD4+ T cells, which probably comprise a lifelong reservoir. The half-life of this reservoir is 44 months, and, according to recent estimates, eradication could take 60-73 years (Finzi et al. 1999). Even after years of sufficient viral suppression to below 20-50 copies/ml, cellular viral transcription still takes place (Dornadula et al. 1999, Furtado et al. 1999, Zhang et al. 1999, Sharkey et al. 2000). This holds in particular for blood cells, but also applies to lymph nodes and sperm (Lafeuillade et al. 2001, Nunnari et al. 2002). Different methods have been used to attempt to flush out these latent reservoirs (IL-2, hydroxyurea, OKT), but all have failed (Kulkosky et al. 2002, Pomerantz et al. 2002). At the last World AIDS Conference, Bob Siliciano painted a bleak picture of the situation (Siliciano 2002): Eradication is not possible with currently available drugs. The reservoirs cannot be eliminated. Latently infected cells differ from uninfected cells only in one minute detail, which is hardly detectable with present methods and cannot be specifically targeted. Flushing out the reservoirs or even just the complete elimination of memory cells is either unsuccessful, too toxic, or far too dangerous. Hopefully, future chapters can be dedicated to this issue.

Other Important Aspects of HAART

Besides the goals described above – virological, immunological and clinical treatment success – several other aspects need to be considered. Although not primary goals of HAART, they are nevertheless extremely important: cost reduction; prevention; and improving compliance – a constant challenge for every HIV clinician.

Reduction of costs

Antiretroviral therapies are expensive. Single drugs cost between \$250 and \$1000 per month, depending on the drug and the country where it is prescribed. Even within drug classes, astonishing differences exist. In some countries, Crixivan[®] is relatively cheap, at roughly half the price of Agenerase[®]. A combination regimen with Trizivir[®] and Kaletra[®] adds up to at least \$2,000 per month. As a health care provider, it is therefore important to have an idea of costs and to question the pricing policy of some pharmaceutical companies. For example, why does boosted Invirase[®] cost nearly twice as much as boosted Fortovase[®] in Germany?

Despite such high costs, the positive effect of HAART remains unquestioned. Reliable estimates assume an expenditure of between \$13,000 and \$23,000 per additional QUALY (quality-adjusted year of life; Freedberg et al. 2001) – relatively cheap in comparison to many other therapies. HAART can avoid expensive treatment of opportunistic infections, hospital and patient care costs. In one German study, between 1997 and 2001, total annual outgoings per patient decreased from €35,865 to €24,482 (Stoll et al. 2002). Many patients are able to work again, resulting in an overall economic reduction of costs (Sendi et al. 1999).

As HAART is expensive, when treatment is being changed, either merely to reduce pill burden or due to concern over long-term toxicity, it is justified to ask a patient to first use up existing stocks. Privately insured patients are obviously appreciative of this, but even patients on state health insurance should be made aware of drug costs – not to cause guilt feelings or to transfer insufficiencies of the health care system to the patient, but rather to create an awareness of the value of this treatment.

Initially, only one box of tablets should be prescribed, even if, for example, one box of Retrovir[®] prescribed at the standard dose – 15 years after licensing! – still only lasts for 20 days. Only by this approach can one avert a patient being left with

many drugs should intolerance occur. Prescribing more than three months of drugs at a time should be avoided.

Prevention

The lower the viral load, the less infectious is the patient. A prospective study of 415 HIV-discordant couples in Uganda showed that of 90 new infections over a period of up to 30 months, none occurred from an infected partner with a viral load below 1500 copies/ml. The risk of infection increased with every log of viral load by a factor of 2.45 (Quinn et al. 2000). In a study from Thailand of 493 patients, this factor was 1.81 – and here no case of infection was recorded below 1094 copies/ml (Tovanabutra 2002). Within limits, HAART can thus serve as a preventive measure (Hosseini et al. 2002).

Most patients are interested in knowing: "Do I still need to use a condom?". The answer is: "Yes!". Studies have shown that the decrease of viral load in plasma and seminal fluid is roughly parallel and that a decrease of several logs in plasma after several months may also be seen in semen (Liuzzi et al. 1999). Although the same seems to be true for the vaginal and anorectal mucosa, individual risk remains difficult to estimate (Lampinen et al. 2000, Cu-Uvin et al. 2000). Furthermore, viral load levels in blood and other body fluids do not always correlate with one another (see also the chapter on "Monitoring").

In recent years the preventive effects of HAART seem to have led to an increase in risk behaviour. Calculations have shown that an increase in risk behaviour of only 10 % would offset the effects of HAART (Blower et al. 2001, Law et al. 2001). In the French PRIMO Cohort, so-called risk contacts of patients increased from 5 % to 21 % between 1998 and 2001 (Desquilbet et al. 2002). Small syphilis endemics among HIV infected individuals are now being reported in every major city in the USA and Europe. Of equal concern is the increasing data on transmission of multiresistant viruses.

Compliance as a goal of therapy

Compliance is the Achilles heel of antiretroviral therapy. Non-compliance is a main, if not the most important, factor in treatment failure. Insufficient plasma drug levels and partial suppression of viral load are the conditions under which resistance can develop.

Compliance is defined as consent and acceptance of a treatment regimen by the patient. In the mid-90s a newer, more politically correct term was adopted – "adherence". This term describes both clinician and patient working together to achieve a treatment concept acceptable for both, and emphasizes, quite correctly, that not only the patient may be responsible for treatment failure. Adherence includes all factors that influence staying on a regimen, in terms of "acceptability". Whichever term is used, two facts remain:

1. If 5 % of drugs are not taken, treatment success becomes precarious.
2. Clinicians usually overestimate the compliance of their patients.

"Risk patients" for non-compliance include not only individuals with substance or alcohol abuse or those experiencing side effects. Studies on compliance have identified both patients with depression or younger age as being particularly at risk (Murri et al. 2001, Frank 2002). Positive factors are physician experience, confidence of the patient in the positive effects of HAART, and social support. Race, sex or stage of disease do not seem to be relevant. The individual's view of disease and health, acceptance of modern medicine and fear of side effects are further considerations. However, all of these factors vary greatly, and in the end compliance is difficult to predict in individual cases (Lerner et al. 1998).

The importance of taking drugs regularly has been demonstrated in numerous studies in recent years. In one study of 99 patients, in which compliance was evaluated by way of an electronic monitoring system, the rate of treatment failure was only

22 % in patients with a level of compliance of at least 95 % (95 % of doses taken). Failure rates in patients with 80-94 % or < 80 % compliance were 61 % and 80 %, respectively. In this study, 41 % of patients were misjudged by their treating clinicians with regard to compliance. Nurses seemed to have a better understanding of their patients, judging incorrectly in only 30 % of cases (Paterson et al. 2000). The importance of compliance is also demonstrated by the successes reported in patients with directly observed therapy (DOT). A DOT study performed in one of Florida's correctional facilities showed 100 % of subjects with a viral load < 400 copies/ml at 48 weeks, compared with 81 % in an unmonitored control group in the general population (Fischl et al. 2001).

Non-compliance not only leads to virological failure. It also has immunological consequences. In an analysis of two prospective studies, patients with a compliance of 100 %, 80-99 % and 0-79 % experienced reductions in viral load by 2.77, 2.33 and 0.67 log after one year. At the same time, the CD4+ cell count rose by 179, 159 and 53, respectively (Mannheimer 2002). Furthermore, non-compliance not only affects CD4+ count and viral load, but also has clinical effects. In a Spanish study, patients who did not take more than 10 % of their drugs had a four-fold increase in mortality risk (Garcia 2002). This data has been confirmed in other studies (Maher et al. 1999, Hogg et al. 2000). Hospital stays are also less frequent in patients with high compliance (Paterson et al. 2000). In addition, it should be considered that the risk of transmission of resistant viruses is increased by non-compliant patients.

The basic mechanisms for development of resistance should be explained to patients. One must emphasize that, in contrast with other chronic illnesses, resistance mutations do not disappear once they have developed. Diabetes and hypertension make effective examples: whereas these diseases may "tolerate" forgetting the occasional tablet, HIV is different – here even short-term lapses can have irreversible consequences. Patients have to be made aware of this unusual feature of HIV disease. Coop-

eration with special treatment discussion groups offered by various support organizations can be useful.

If compliance remains low

Despite all our efforts, some patients will not be able to improve their compliance. Physicians and other health care providers are advised not to take this personally or to feel offended should a patient not want to participate in the advances of medicine. Even if it may be difficult to accept others' views on life and treatment, tolerance and acceptance should remain fundamental to the interactions of all health care providers with their patients. Some providers, especially those who treat selective patient populations in university settings, sometimes forget the reality of routine medical practice. Rigidly upholding the principles of modern medicine usually doesn't help here, and putting patients under pressure achieves even less.

The question of whether non-compliant patients should continue to be treated with antiretroviral therapy is not always easy to address. On the one hand, there are patients who benefit even from suboptimal therapy; on the other hand, drugs are expensive and should not be prescribed too readily. When resources are limited, available drugs should be used prudently. One should also be beware of criminal dealings: there have recently been several reports of patients who had deals with pharmacies in order to receive other drugs (methadone, etc.), or even money, in exchange for their prescriptions (black sheep are ubiquitous!). Prescriptions have to be documented in the patient chart. Where there are good reasons to doubt the compliance or honesty of a patient, plasma drug levels can be determined.

Twelve tips to improve compliance

1. Every patient should receive a written (legible!) treatment plan, which should be reviewed at the end of the visit. It should include a telephone number to call in case of problems or questions.
2. Patient and clinician should agree on the treatment plan. The patient's concerns or critical questions should be discussed.
3. The patient should have the impression that the treatment regimen was not randomly chosen, but tailored to his/her individual needs.
4. The explanation of a new or modified treatment plan takes time, and should not be rushed – all questions should be answered.
5. The reasons why compliance is so important should be explained. It makes sense to repeat such conversations – they should not only take place when initiating or modifying treatment, but should be part of routine care.
6. Possible side effects should be explained, as well as what can be done to alleviate them.
7. Support groups and other types of assistance should be utilized and offered.
8. It is important to tell the patient to come back if any problems are encountered with HAART – it is better to solve them together than have the patient try to deal with them alone at home.
9. The patient should know that the treatment regimen must be taken in its entirety ("Last month I left out the big tablets").
10. Prescriptions should be documented, in order to get a rough idea of compliance. Irregularities should be addressed openly.
11. Especially during the early phases of therapy, the patient should be informed of treatment success as seen by reduction of viral load and rise in CD4+ count.
12. Treat depression!

Duesbergians

A special case is presented by patients who refuse all antiretroviral therapy on principle. These patients are often being treated by doctors who call themselves "Duesbergians" (after Peter Duesberg, a U.S. virologist and AIDS dissident, who denies the link between HIV and AIDS). It can be distressing to stand by and watch these patients rush headlong into ruin. Counselling should be detailed, and with written documentation where possible. Here is an example from everyday practice in 2001:

A patient about 40 years old presents with established but as yet untreated HIV infection of many years standing. He has 30 CD4+ T cells/ μ l and toxoplasmosis encephalitis, which resolves substantially after 4 weeks of acute treatment (there are still isolated lesions visible in the last MRT). On the day of his discharge, the patient is clinically in fairly good condition, with fully intact orientation. He categorically objects to the initiation of antiretroviral therapy, which is being urgently recommended to him. His primary care provider had advised him against any HIV treatment ("one can die from AZT therapy; the other drugs are not much better"), and he objects to antibiotics anyway. For this reason he will not continue the secondary prophylaxis for toxoplasmosis, and, furthermore, he has had diarrhea (cryptosporidia?), skin problems (seborrheic dermatitis, thrush) and significant weight loss (MAC?) since his first day in hospital. After all, what he now needed was to recuperate.

In such cases we have asked patients to confirm by signature that they have received informative counselling. Every patient may and should decide for himself (if he is fully oriented), but he must be adequately informed of the consequences of his actions. It is important to get the message across to the patient: if he changes his mind (when the toxoplasmosis relapses!), he can come back! However, medical debate with Duesbergian doctors is in our experience unfruitful and merely a waste of time and energy.

Luckily, such cases are less frequent today. The initial scepticism with regard to HAART declined significantly in the light of the overwhelming successes in recent years. And, there is (thank

goodness) now less hype about Peter Duesbuerg, at least with respect to his HIV activities. The sect is diminishing.

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4. When to Start HAART

Christian Hoffmann

"It's the most important question in HIV therapy" (A. Fauci)

The indication for antiretroviral therapy is based on clinical assessment, CD4+ cell count, and viral load. These three important factors determine whether therapy should be started, or if it can still be delayed. At first glance, it appears straightforward: the lower the CD4+ count and the higher the viral load, the higher the risk of AIDS (Mellors et al. 1997, Lyles et al. 2000), and the more urgent the indication for treatment.

Nevertheless, the best time for initiation of therapy is the subject of controversial debate. The risk of AIDS must be weighed against the risks of long-term toxicity and resistance. After the "hit hard and early" dogma of 1996, which recommended therapy from the earliest stages of infection, many health care providers have now become more hesitant. Concern over long-term toxicity and the realization that eradication cannot be achieved in the foreseeable future have led to less rigid guidelines (US: Yeni et al. 2002, British guidelines: HIVA 2001, <http://www.bhiva.org/guidelines.pdf>).

Guidelines merely provide points of reference and are not set in stone. Decisions must be made on a case by case basis, even if some health insurance providers tend to ignore this and use such guidelines to their advantage. In some cases, therapy may start earlier than recommended in the guidelines; in other cases, therapy might (or even should) be delayed. Some national guidelines recommend treatment earlier (US guidelines; Yeni et al. 2002) than others. The British guidelines (BHIVA 2001), in particular, recommend delaying treatment until the CD4+ count is $< 200/\mu\text{l}$ (or following a rapid decrease).

Table 4.1: When to start treatment: summary of recommendation

British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy*

Presentation	Surrogate markers	Recommendation
Primary HIV infection		If treatment considered, start as soon as possible, certainly within 6 months of contracting HIV; clinical trial if available
Established asymptomatic HIV infection	CD4 count >350 cells/ μ l and any viral load	Defer treatment
	CD4 count 200-350 cells/ μ l	Start treatment within this range, taking into account the rate of CD4 decline, symptoms, patient's wishes and viral load
	CD4 count <200 cells/ μ l and any viral load	Treat
Serious/ recurrent HIV related illness or AIDS		Treat

* BHIVA Writing Committee on behalf of the BHIVA Executive Committee. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. HIV Med 2001; 2:276-313.

Experiences from Daily Practice

Even if the indication for HAART seems obvious, a conversation with the patient should clarify whether he or she is indeed prepared to start treatment. The problem is not to start HAART, but to continue it, day after day, month after month. The decision to initiate treatment is often made prematurely. In some cases, patients put themselves under pressure unnecessarily, or let others do so. A single lower CD4+ count, a prolonged flu seeming to indicate a weakened immune system ("I never had anything like that before"), springtime lethargy, new study results, a promising new drug in the newspaper ("I've heard so much about T-20"), a partner who has started therapy – none of these are indications for initiation of treatment.

As a rule, time should be taken before starting therapy. The well-informed patient has the best compliance! We recommend

that patients come for several consultations to prepare for treatment. There are two exceptions: patients with an acute HIV infection, and those with severe immunodeficiency or AIDS. But even in the presence of most AIDS-defining conditions, the acute disease can often be treated first before initiating antiretroviral therapy a few days later. If a long vacation has been planned, and the test results are not too bad, it is better to delay therapy until such time as treatment success and side effects can be monitored. On the other hand, patients may often find one reason after another (stress at work, exams, change of job etc.) to delay initiation of treatment. They may have irrational fears or simply false expectations of HAART and its consequences – starting therapy does not mean that one is no longer able to work!

Starting Therapy in Symptomatic Patients

There is currently consensus that every symptomatic patient should receive antiretroviral therapy. All opportunistic infections indicative of severe immunodeficiency, such as CMV, MAC, toxoplasmosis or PCP, and also AIDS malignancies, should therefore prompt rapid initiation of therapy, especially if there is no specific treatment available, as in the case of PML.

However, the term "symptomatic" which commonly applies to patients in WHO Stage C (with AIDS) and in Stage B (symptomatic, but without AIDS), can be confusing. Herpes zoster (Stage B) may occur even with a slight immune defect and does not necessarily indicate immunological deterioration. Thrombocytopenia or constitutional symptoms may also have other causes. A further example: Tuberculosis, which is an AIDS-defining illness and therefore implies an indication for therapy, is a facultative opportunistic infection. It may occur without or with only moderate immunodeficiency. In our experience, one is justified in waiting with HAART in a patient with good CD4+ cells. The British treatment guidelines (<http://www.bhiva.org/guidelines.pdf>) specifically mention pulmonary tuberculosis as being a possible exception in which

treatment may be deferred. A relevant case study is outlined in the following table.

Table 4.2: Case study, in which treatment in accordance with the guidelines could have led to more than seven years of over-treatment (and presumably to resistance mutations).

		CD4+ (%)	Viral load
May 95	Pulmonary tuberculosis (= AIDS)	330 (27)	NA
Feb 96	End of tuberculosis treatment	437 (29)	NA
	Patient refuses (urgently recommended) HAART		
Oct 97	Patient refuses (urgently recommended) HAART	402 (33)	29,500
Oct 98	Patient refuses (urgently recommended) HAART	440 (30)	13,000
Oct 99	Patient refuses (urgently recommended) HAART	393 (29)	13,500
Oct 00	Patient refuses (recommended) HAART	520 (30)	12,500
Jun 02	Doctor does not want to start HAART	521 (29)	7,440

NA = not available

On the other hand, we recommend that patients with Hodgkin's disease, which does not appear in any guidelines, should definitely be treated with HAART, irrespective of CD4+ cell count (Hoffmann et al. 2002).

Starting Therapy in Asymptomatic Patients

The cut-off of 350 CD4+ cells/ μ l is important in many guidelines. Above 350 CD4+ cells/ μ l, the scheme is relatively simple: Wait. Severe complications are rare at this stage. Few data exists concerning patients with >350 CD4+ cells/ μ l; a single matched-pair analysis from Switzerland indicated a small, though significant, clinical benefit if HAART was started above this level (Opravil et al. 2002, see below).

Many clinicians now prefer to start HAART at a later date. Disagreement has developed among many experts. Much of what is currently being debated, ranging from unrelentingly strict

treatment to an exaggeratedly relaxed view on therapy, is based largely on subjective opinion, perhaps own experience, and often merely polemics.

Is virological response less durable with a low CD4+ cell count and a high viral load?

At first glance, many cohort studies have demonstrated that virological response is less if the CD4+ count at initiation of treatment was low and the viral load high (Casado et al. 1998, Mocroft et al. 1998 and 2000, Miller et al. 1999, Wit et al. 1999, Deeks et al. 1999, Chaisson et al. 2000, Grabar et al. 2000, Le Moing et al. 2000, Yamashita et al. 2001, Skowron et al. 2001). It might appear straightforward: the higher the viral load and the lower the CD4+ count, the less the virological success of HAART. Defenders of early initiation of HAART often cite this data. They forget three important points:

First, this is not true for the two large cohorts in which only treatment-naïve patients were studied (Cozzi Lepri et al. 2001, Phillips et al. 2001). These confirm our observations that even a treatment-naïve patient with a high viral load and a low CD4+ counts has good chances of sufficient and long-term suppression of viral load. Under these circumstances, the initial lab values are less important – if the patient is compliant! Even in the French APROCO Cohort, in which greater differentiation existed between treatment-naïve and treatment-experienced patients (Le Moing et al. 2002), treatment-naïve patients with a high viral load at baseline showed at most an insignificant negative trend. That viral load and CD4+ count have predictive values in all cohort studies in which most (up to 91 %) patients included were usually pre-treated with NRTIs, indicates one thing: In patients with prolonged mono or dual therapy, virological success of HAART may be compromised. Previous nucleoside analog therapy has been a risk factor for virological treatment failure in many cohorts (Casado et al. 1998, Deeks et al. 1999, Chaisson et al. 2000, Grabar et al. 2000, Le Moing et al. 2002). As, fortunately, there are now very few patients on

mono or dual therapy who have to change to HAART, it is justified to concentrate exclusively on treatment-naïve patients.

Secondly, the relative risk for virological failure was often only increased in patients with substantial immunosuppression ($< 50\text{--}100$ CD4⁺ cells/ μl) or very high viral load ($> 100,000$ copies/ml). At levels above 200 CD4⁺ cells/ μl or a viral load of less than 100,000 copies/ml, differences could generally not be detected (see below).

Thirdly, hardly any of these studies considered compliance. A patient who starts HAART under emergency conditions at 30 CD4⁺ cells/ μl (and who presumably went to the physician only shortly before or even after clinical manifestation of AIDS) may have a different idea of sickness and health and may be less compliant than someone who seeks medical advice with a good CD4⁺ count and begins HAART after thorough reflection. Adherence was an important predictor in one of the few studies in which it was included (Le Moing et al. 2002).

Is immunological response less durable with a low CD4⁺ cell count and a high viral load?

Multiple factors influence the increase in CD4⁺ cells: duration of immunosuppression, age, thymus size or extent of thymus degeneration. Do these include baseline values at initiation of therapy? Astonishingly, several cohorts found no association between them (Yamashita 2001, Pezzotto et al. 2001, Cozzi-Lepri et al. 2001). However, these studies all showed that the rise in CD4⁺ cells is similar, although levels remained less with an initially low CD4⁺ count. Also in our experience, immune reconstitution is rarely complete after low initial values; the more damaged the immune system, the less likely a complete recovery. In the Swiss Cohort, low CD4⁺ count at baseline was a clear risk factor for not attaining 500 CD4⁺ cells/ μl after four years (Kaufmann et al. 2002). There is also concern over the 10–15 % of patients with a discordant response, where HAART is virologically extremely successful, but CD4⁺ count remains low (Piketty et al. 1998, Renaud et al. 1999).

Late initiation of therapy may further mean that antigen-specific immune reconstitution remains impaired, both against HIV, and opportunistic and other pathogens. Numerous studies suggest that qualitative immune reconstitution does not initially occur at the same pace as quantitative reconstitution (Gochorov et al. 1998, Tortatjada et al. 2000, Lederman et al. 2001, Lange et al. 2002). One can make the analogy with a patch of desert where weeds will grow before flowers. So, what are the clinical consequences of these lab data? Why does AIDS resolve so impressively and rapidly with rising CD4+ cells? Why can even severely immunodeficient patients discontinue their anti-infectious prophylaxis quite safely, once their CD4+ count has risen to $> 200/\mu\text{l}$? These clinical observations – at least in the short term – seem to contradict the limited extent of immune reconstitution currently observed.

When does the risk of clinical progression remain high even after starting HAART?

Almost all studies demonstrate a clear correlation between CD4+ count at initiation of HAART and rates of both AIDS and death (Hogg et al. 2000, Grabar et al. 2000, Cozzi-Lepri et al. 2001, Kaplan et al. 2001, Phillips et al. 2001, Sterling et al. 2001, Egger et al. 2002). Especially patients with a very low CD4+ count ($< 50/\mu\text{l}$) continue to be at high risk for AIDS (Hogg et al. 2000). In other cohorts, the risk continued to be elevated even below a CD4+ count of 200 cells/ μl (Phillips et al. 2001, Sterling et al. 2001). An Italian cohort showed that increased risk of clinical progression was associated with a CD4+ count that did not rise and remained below 50 CD4+ cells/ μl (Cozzi Lepri et al. 2001).

The largest study to date on this topic was published in 2002 by the ART Cohort Collaboration. Here, several cohorts were pooled and almost 13,000 patients on HAART were analysed. The data seems clear-cut (Egger et al. 2002). Baseline CD4+ count correlated highly with the probability of AIDS or death. Compared to patients who had started HAART below 50 CD4+

cells/ μ l, risks were significantly lower in patients with higher levels of T helper cells (see the following table).

Table 4.3: Risk of progression in the ART Cohort Collaboration (Egger et al. 2002)

Baseline CD4+ cells/ μ l	Relative risk
50-99 versus < 50	0.74 (0.62-0.89)
100-199 versus < 50	0.52 (0.44-0.63)
200-349 versus < 50	0.24 (0.20-0.30)
> 350 versus < 50	0.18 (0.14-0.22)

One should note the moderate difference between the groups above 200 CD4+ cells/ μ l. Viral load at baseline was only relevant if it was at a very high level, i.e. above 100,000 copies/ μ l.

All cohorts showed very low rates of morbidity and mortality. However, the observation periods were usually short and lasted less than three years. In the long run more significant differences may be demonstrated.

Below 200 CD4+ cells/ μ l

The available cohort studies provide relatively clear evidence for initiation of treatment below 200 CD4+ cells/ μ l – the threshold value, below which treatment should no longer be delayed. Logically, the more significant the immune defect, the longer it takes for the situation to improve on HAART, and until then patients are still at risk. A devastated immune system cannot recover quickly.

However, even under these circumstances, the risk of AIDS after initiation of HAART is only slightly elevated. In an analysis of treatment-naïve patients from the three large European cohort studies - the Swiss Cohort, the Frankfurt Clinic Cohort and the EuroSIDA – in patients with less than 200 CD4+ cells/ μ l at initiation of treatment, 8.3 new AIDS diagnoses per 100 patient years were recorded ; with > 350 CD4+ cells/ μ l the incidence was 1.8/100 patient years. The mortality rates were 2.9 versus 0.7/100 patient years.

Below 200 CD4+ cells/ μ l, the risk of severe infections increases with time, and rapid initiation of HAART becomes a matter of urgency. But, even in such cases, it is a matter of weeks rather than days. We have now made it our practice to start PCP prophylaxis in patients presenting for the first time with < 200 CD4+ cells/ μ l. The first two to three weeks are used for diagnostic procedures (fundoscopy, chest X-ray, ultrasound) and to provide informative counselling. Whether the patient might be a candidate for enrolment in a clinical trial is also considered, and we try to attain an impression of the individual's psychosocial situation (see Chapter 5). HAART is started only when these issues have been addressed.

Table 4.4: Studies on the influence of baseline CD4+ count on treatment success in patients with 200-350 CD4+ cells/ μ l and in patients with > 350 CD4+ cells/ μ l at initiation of HAART.

	Less AIDS, deaths?	More pronounced increase in CD4+ cells?	Improved virological response?
Canadian Cohort (Chaisson 2000, n=553)	NA	NA	No (trend)
Italian Cohort II (Cozzi Lepri 2001, n=1.421)	No	No	No
CDC database, USA (Kaplan 2001, n=10.885)	No	NA	NA
Baltimore Cohort (Sterling 2001, n=530)	No	NA	NA
Swiss, Frankfurt, EuroSIDA Cohorts (Phillips 2001, n=3226)	No	NA	No
Swiss Cohort (matched pair analysis subgroup) (Oprivil 2002, n=2x283)	Yes RR = 2.10	NA	NA

NA = not available

Above 200 CD4+ cells/ μ l

Above 200 CD4+ cells/ μ l the situation becomes more complicated. Most studies have not yet been able to provide evidence for the benefit of starting therapy early (above 350 CD4+ cells/ μ l). The table below summarises studies on this topic.

In the meta-analysis of the three large European cohorts cited above, the difference was minimal. The AIDS-rate was 2.3 versus 1.8, the mortality rate 1.0 versus 0.7 per 100 patient years. This means one more case of AIDS in 200 patient years! Vast randomised studies would probably be necessary to detect a difference between the two patient groups.

Surprisingly, a case-control study from Switzerland did show a relevant difference (Opravil et al. 2002). 283 patients, who were started on HAART with a count above 350 CD4+ cells/ μ l, were matched by age, sex, CD4+ count, viral load and risk group for HIV infection with control patients who had been untreated for at least 12 months. At follow-up around three years later, the AIDS risk was more than twice as high in the untreated group. Those in favour of starting treatment early will find plenty of supporting arguments in this study. However, besides considerable methodological problems due to the design of this study, one challenging question remains when looking more closely at the 42 CDC Category B illnesses and 10 AIDS cases which occurred additionally in the untreated group: Are OHL (8 cases), oral thrush (10), herpes zoster (9), thrombocytopenia (9), and a few cases of tuberculosis, pneumonia and Candida-esophagitis worse than the side effects of antiretroviral therapy? Over one third (35 %) of treated patients discontinued HAART, 51 due to gastrointestinal complaints, 25 due to CNS or renal problems, or lipodystrophy. Is there really clinical benefit in starting treatment early? If one takes into account the toxicity of the drugs and the associated reduction in the quality of life, this benefit seems to come at quite a high price.

All in all, the available results, despite their limitations, do support the current trend of delaying initiation of therapy above

200 CD4+ cells/ μ l. According to the US-Guidelines, the following points should also be considered in patients with 200-350 CD4+ cells/ μ l, in addition to a high viral load ($> 50,000$ copies/ml): rate of CD4+ cell loss (e.g. > 100 /year); potential adherence; individual patient risk for toxicity (Yeni et al. 2002).

This risk assessment will change as soon as combinations with better long-term tolerability become available. The evaluation of the indication for treatment must therefore continually be re-examined in the light of new developments.

Practical tips for starting therapy in asymptomatic patients

- Below 200 CD4+ cells/ μ l treatment should be started as soon as possible. However, even here, one should take the time, to get acquainted with the patient, give proper counselling and first begin with prophylaxis or diagnostic procedures (fundoscopy!) – it's not usually a question of having to start within a few days!
- Above 200 CD4+ cells/ μ l, there is more time – the individual history of the patient has to be taken into account.
- A decrease of more than 80-100 CD4+ cells/ μ l per year is too much! Don't delay too long!
- There is considerable variability in laboratory values. Therefore, a single CD4+ count (especially when in the range of 200-350/ μ l) should always be repeated before starting treatment.
- Above 350 CD4+ cells/ μ l: Wait. Monitor at least every three months.
- The higher the viral load, the more frequent checks of CD4+ count are necessary: at a viral load > 50,000 copies/ml controls should be performed at least every two months.
- Initiation of treatment may be justified at levels above 350 CD4+ cells/ μ l – if the viral load is very high, the CD4+ count is decreasing rapidly or the patient requests it (after careful counselling).
- Check ahead of time whether a patient may be suitable for enrolment in a clinical trial.

Arguments for and against an EARLY start (> 350 CD4+ cells/ μ l)

- "The lower the CD4+ count, the longer the patient will remain at risk later."

(Counter: This statement applies mainly to patients with substantial immunosuppression in whom therapy initiation is not debated. The earlier one starts, the more long-term toxicities will occur!)

- "A lower CD4+ count often implies that only moderate immunological-virological treatment success is possible – at some stage, the destruction of the immune system is irreversible."

(Counter: This is mainly true for patients with substantial immunosuppression. However, the virological response does not seem to be reduced in treatment-naïve patients.)

- "The longer one waits, the fitter the virus becomes via generation of quasispecies and immune escape variants, and the more difficult it is to treat."

(Counter: Interesting laboratory hypothesis. But, where's the relevant clinical data?)

- "The worse the condition of the patient, the worse the tolerability of HAART."

(Counter: Ancient, proven medical wisdom. But, does it apply here, where we are referring to asymptomatic patients?)

- "HIV should be treated as early as possible, as any other infectious disease."

(Counter: HIV is not akin to any other infectious disease. HIV cannot be cured like many bacterial infections. Herpes

viruses, for which there is no cure, are also treated only as needed.)

- "It has been proven that patients are less infectious on treatment."

("Counter: And may be more prone to risk behaviour. In addition, the risk of transmission of primary resistance mutations increases.")

Arguments for and against a LATE start (< 200 CD4+ cells/ μ l)

- "The earlier one starts, the sooner and more certain the side effects."

(Counter: This may be true. The question is: Does one more year without therapy but with increasing risk of AIDS, really make a difference?)

- "The earlier one starts, the higher the risk for resistance in the long-term."

(Counter: OK, but... compliant patients, who have sufficient suppression of viral load, have good chances of not developing resistance, even over many years.)

- "Even a bad immune system can regenerate; after all, prophylaxis can be safely stopped after a rise in CD4+ count."

(Counter: This may be true for some patients, but not for all. There are indications that the qualitative response remains impaired.)

- "It is never too late to start therapy between 200-350 CD4+ cells."

(Counter: *Who can be so sure? Some AIDS defining diseases may rarely occur even in this scenario; there is no certainty that PML or lymphoma might not develop – and should they, good advice is hard to find.*)

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5. How to Start with HAART

Christian Hoffmann

A Practical Approach to the First Regimen – Important Rules

The most common initial regimens consist of two nucleoside analogs, combined with either a (possibly boosted) PI, an NNRTI or a third nucleoside analog. No one combination has clearly been shown to be superior to another, and in a meta-analysis (and also a good review) of 23 clinical studies in 3257 patients, virological and immunological effects were comparable for most regimens. An important factor was simply the number of pills – the less pills, the better. Pill burden is therefore an important consideration when choosing a treatment regimen (Bartlett et al. 2001).

The choice of regimen may frequently be adapted to the patient's individual needs with respect to compliance, concurrent illnesses and concomitant medication. However, the simplest therapy may not be the best.

Ten important points to consider for the initial regimen:

1. The first shot must be a good shot, i.e. viral load must decrease – and be undetectable by 3-6 months at the latest.
2. The initial regimen should ideally have to be taken only two times a day.
3. If there are problems with compliance, once-daily regimens should be considered (even although there is as yet limited data on them).
4. Initial therapy should not consist of all three drug classes, in order to keep further options open for later.
5. Care should be taken to avoid overlapping toxicities – several allergenic drugs should never be given at once.

6. Each patient should receive the ART he is able to take!
7. Don't insist on theoretically superior combinations, if reality compels another decision.
8. All drugs should be started on the same day – no lead-in mono- or dual therapy!
9. All patients, especially if treatment-naïve, should be encouraged to participate in clinical trials!
10. Pros and cons of different combinations should be discussed with the patient; there is usually enough time.

What Should Be Clarified Beforehand?

Dosing issues

Can the patient really take drugs twice, three, or even four times a day? Is this realistic with regard to the individual professional or social situation? If in doubt, a simpler regimen is preferable to one that is presumed to be more effective. Many i.v. drug users cannot be expected to take ten or twenty tablets a day over years, following a strict protocol. But such patients also need treatment, and studies with combinations that allow once daily dosing are underway. Successful once-daily regimens for i.v. drug users in the form of DOT (Directly Observed Therapy) have been described (Haberl et al. 1998, Proenca et al. 2000, Conway et al.).

For many patients, the number of pills or requirements for food intake are decisive. The range of licensed and recommended initial regimens varies from 2 to 16 pills per day. Many find it unacceptable to have to take pills at certain times during the day, on an empty stomach, or with fatty foods. Patients today are also more demanding than three or four years ago – justifiably so! Even the size of tablets can be a problem for some patients. Such issues must be discussed *before* initiating therapy.

Concurrent illnesses

Every patient must be thoroughly questioned and examined with regard to possible concurrent illnesses before starting treatment. In particular, chronic hepatitis has to be considered when choosing a regimen. The risk for severe hepatotoxicity on nevirapine or ritonavir is highest in such patients (Den Brinker et al. 2000, Martinez et al. 2001, Saves et al. 1999, Sulkowski et al. 2000 + 2002). Other illnesses must also be borne in mind (see table below).

Table 5.1: Concurrent illnesses requiring caution with specific drugs. These recommendations are not absolute contraindications.

Illness	Caution with
Active hepatitis C	Nevirapine, boosted PIs
Active hepatitis B	Nevirapine, boosted PIs (In contrast: lamivudine and tenofovir seem to be beneficial!)
Anemia	Zidovudine, possibly also lamivudine
Polyneuropathy	Stavudine, zalcitabine, didanosine
Kidney disease	Indinavir, possibly also tenofovir
Diabetes mellitus	PIs (especially if a NIDDM is at risk of becoming an IDDM!)
Arterial hypertension	Indinavir
Myocardial infarction	PIs (potentially beneficial: nevirapine)
Psychosis, other CNS illnesses	Efavirenz
Chronic diarrhea	Nelfinavir, other PIs
Active substance abuse, substitution	Probably no NNRTIs, no ritonavir

Interactions with medications and drugs

Interactions are important in the choice of combination regimens. Whereas interactions between antiretroviral drugs are well known, interactions with other concomitant medications are often less well characterized. The urgent need for more research was recently demonstrated in a study, in which the interactions of HAART and statins were investigated. In healthy volunteers, measurement of plasma levels showed elevated lev-

els of simvastatin by 3059 % after concurrent dosing with ritonavir or saquinavir (Fichtenbaum et al. 2002). Many drugs should be avoided in combination with particular antiretroviral drugs, as incalculable interactions may occur. These include certain contraceptives (the Pill). If myelotoxic drugs (ganciclovir!) have to be co-administered, care should be taken with zidovudine. Patients receiving aciclovir suffer kidney problems from indinavir significantly more often than those with normal renal function (Herman et al. 2001). Warfarin can also be a problem – ritonavir can significantly lower plasma levels (Libre et al. 2002). Further typical “problem drugs” include migraine remedies and prokinetic drugs and sedatives. Not every substance can be discussed here. Many are described in the respective chapters. In individual cases, the package insert should be checked. If the medication is already being taken, initiation of HAART provides a good opportunity to re-evaluate the existing regimen.

Drugs or alcohol can also interact with HAART. For those in substitution programs, the methadone requirement may be significantly increased by certain antiretroviral drugs such as nevirapine and efavirenz. To a lesser extent, this is also true for ritonavir and nelfinavir. Other combinations may lead to even more dangerous effects. Several deaths have been reported after simultaneous dosing with ritonavir and amphetamines or ecstasy, or the popular narcotic gamma hydroxybutyric acid (GHB, Samsonit® or “liquid ecstasy”; Hales et al. 2000, Harrington et al. 1999). Ritonavir in particular can inhibit metabolism of various drugs such as amphetamine, ketamine or LSD (excellent review in: Antoniou et Tseng 2002). Clinician and patient are well-advised to have an open conversation about drug use before starting therapy. Marijuana and THC appear to have a low potential for interactions (Kosel et al. 2002).

Which Drug Classes Should Be Used?

All combinations currently used as initial regimens consist of two nucleoside analogs plus either a PI, an NNRTI or a third

nucleoside analog. Any other combinations are experimental or not justified for use outside the framework of clinical studies. Advantages and problems of these three strategies are outlined in the table below.

Two nucleoside analogs plus a PI

Only the combination of two nukes plus one protease inhibitor is supported by data from randomized studies with clinical endpoints (Hammer *et al.* 1997, Cameron *et al.* 1998, Stellbrink 2000). Most importantly, data is available over longer periods than for other combinations. These regimens, however, often involve a considerable pill burden and relatively frequent side effects, which makes compliance difficult. They are possibly quite robust with regard to immunological efficacy (Kaufmann *et al.* 2000) – which has yet to be demonstrated for NNRTIs or nukes.

Two nucleoside analogs plus an NNRTI

NNRTIs have an equal, if not presumably even superior, efficacy on surrogate markers as PI combinations. Efavirenz proved more effective than indinavir in the randomized, double-blind 006 Study. However, this study had a high drop-out rate, which possibly influenced results in favor of efavirenz (Staszewski *et al.* 1999). In a cohort analysis, efavirenz was virologically, but not immunologically or clinically superior to a PI (Friedl *et al.* 2001). In the ACTG 384 Study (see below), efavirenz was more effective than nelfinavir. In the Spanish open-label, randomized COMBINE Study, there was a trend in favor of nevirapine compared to nelfinavir, but the difference was not significant (Podzamczar *et al.* 2002). In the Atlantic Study, no difference between nevirapine and indinavir could be shown. Advantages of NNRTI-regimens are low pill burden and good tolerability. In contrast to PIs, however, data with clinical endpoints is unavailable. Neither is there any long-term data or studies on severely immunocompromised patients. A disadvantage of NNRTI combinations is the rapid development of cross-resistance.

Table 5.2: Combining drug classes: Advantages and disadvantages

2 Nukes + PI	2 Nukes + NNRTI	2 Nukes + 3rd Nuke
↑ a lot of data, with clinical endpoints and in significantly immuno-compromised patients	↑ equivalent, perhaps even better suppression of viral load than with PIs	↑ very low pill burden, easy dosing
↑ long-term data available	↑ low pill burden! once-daily may be possible	↑ leaves many options
↑ high genetic barrier for resistance (several resistance mutations necessary)	↑ leaves PI options	↑ few interactions
↓ high pill burden, partly strict dosing requirements	↓ clinical effect not proven (only surrogate marker studies)	↓ probably less potent, especially with higher viral load
↓ frequent drug interactions	↓ no data in severely immunocompromised patients	↓ no clinical endpoints, no long-term data
↓ some PIs with cross-resistance leaves limited options	↓ rapidly occurring complete cross-resistance	
↓ long-term toxicity, lipodystrophy, dyslipidemia	↓ strict monitoring required initially (esp. nevirapine), allergies frequent	

Three nucleoside analogs

AZT+3TC+abacavir (Trizivir[®], see below) is the most investigated triple NRTI combination and is now available as a single tablet. At least two studies have shown that in patients with a high viral load (> 100,000/ml), efficacy was inferior to PI-combinations (Staszewski et al. 2001, Vibhagool et al. 2001). The triple combination therefore seems slightly less potent. Data on other triple nuke combinations has also been published. The Atlantic Study provided extensive controlled data on d4T+ddI+3TC, and results also exist for AZT+ddI+3TC, for example (Lafeuillade et al. 1997). We have had good experience with d4T+ddI+abacavir (Hoffmann et al. 2000). In the randomized CLASS Trial, the combination of

d4T+3TC+abacavir also proved quite effective (Bartlett et al. 2002). In addition to less potential for drug interactions, a triple-nuke-regimen also has the advantages of a low pill burden and enabling NNRTIs and PIs to be spared for later regimens.

Studies comparing these three different initial strategies have been rare. Understandably, pharmaceutical companies show limited interest in risking establishing the inferiority of one of their own products. Such studies are therefore usually performed independently, but are usually slower and sometimes not as well monitored.

Atlantic Study: 298 patients were randomized open-label to receive d4T+ddI+3TC versus d4T+ddI+nevirapine versus d4T+ddI+Indinavir (Squires et al. 2000). After 48 weeks, 49 %, 49 % and 40 %, respectively, of patients reached a viral load < 50 copies/ml in the ITT analysis. In the “on-treatment” analysis (drop-outs not included), however, a significant difference in favor of indinavir over 3TC, a trend for nevirapine over 3TC and no differences between nevirapine and indinavir were shown. For high viral loads (upper quartile), the ITT analysis revealed a viral load under the level of detection in 48 %, 28 % and 26 % of patients, respectively. These differences were not significant. The design of the study did not enable the detection of significant differences.

ACTG 384: This ongoing trial is intended to address several relevant issues: Is a quadruple regimen better than a triple regimen? Are PI-containing regimens superior to NNRTI-containing regimens? Are there differences between d4T+ddI and AZT+3TC as nuke backbones? A total of 980 patients were randomized to six treatment arms (Robbins et al. 2002, Shafer et al. 2002): either AZT+3TC or d4T+ddI combined with efavirenz, nelfinavir or efavirenz+nelfinavir. The nucleoside analogs are blinded; the other drugs are being given open-label. Preliminary data after an average follow-up of 28 months (with a relatively high number of drop-outs) is just as interesting as it is confusing. AZT+3TC was more effective than d4T+ddI, but

only in combination with efavirenz, not with nelfinavir. Conversely, efavirenz was superior to nelfinavir, but only with AZT+3TC as a backbone. The quadruple regimen was better than all triple regimens, but not in comparison to the single most effective regimen of AZT+3TC+efavirenz. The latter, however, led to premature discontinuation in a relatively high number of patients. Toxicity of d4T+ddI was higher than that of AZT+3TC.

CLASS Trial: This study is also ongoing. On a backbone of ABC+3TC, the following three classes are being tested: amprenavir/ritonavir as a boosted PI combination, efavirenz as an NNRTI, and stavudine as a third nucleoside analog. Data from the first 48 weeks is now available for 297 patients (Bartlett et al. 2002). In the viral load assay with a detection limit of 400 copies/ml, the differences between individual study arms have not been significant. However, the ultrasensitive assay has shown a significant difference in favor of the NNRTI arm. Even in a subgroup of patients with a viral load > 100,000 copies/ml, the results from patients receiving the NNRTI arm were superior. Interestingly, no difference could be shown between the other two arms (boosted PI-regimen versus triple nuke), although the virological failure rate appeared to be relatively high in the triple nuke arm.

INITIO: This is a multinational trial among almost 1,000 patients, using various approaches in an open-label, randomized study. The main groups are d4T+ddI plus either efavirenz, nelfinavir or efavirenz+nelfinavir. Second-line regimens are also pre-determined. First results from this study, which is planned to extend over several years, are expected during 2003. The main disadvantage to this study is that the treatment regimens being studied have become somewhat outdated, and consequently there will probably be high drop-out rates. (More information can be found at the website <http://hiv.net/link.php?id=165>.)

Recommended Initial Regimens at a Glance

Possible combinations for initial therapy are shown in the table 5.3.

Table 5.3: Recommended antiretroviral agents for initial treatment of HIV infection*

Recommendation	Column A	Column B
Strongly recommended	Efavirenz	Zidovudine plus lamivudine
	Nevirapine	Stavudine plus lamivudine
	Nelfinavir	Zidovudine plus didanosine
	Ritonavir plus indinavir	
	Ritonavir plus lopinavir	
	Ritonavir plus saquinavir	
Recommended as alternatives	Abacavir**	Didanosine plus lamivudine
	Indinavir	(Stavudine plus didanosine)

* Combining US, UK and German guidelines. For details of the US guidelines, see "Guidelines for Using Antiretroviral Agents Among HIV-Infected Adults and Adolescents", MMWR 51(RR07), <http://hiv.net/link.php?id=214>; for the British Treatment Guidelines, see <http://hiv.net/link.php?id=217>.

** No sufficient data exists on abacavir apart for its fixed combination in Trizivir®.

Of note, many other combinations are possible. They may be acceptable in individual cases or in investigational studies, but general recommendations for their use cannot be given.

Initial therapies currently unacceptable include full dosage ritonavir (because of side effects) or unboosted amprenavir or saquinavir (high pill burden). There is also no sufficient data on boosted amprenavir as initial therapy. Delavirdine and tenofovir are not licensed for initial therapy. As yet no sufficient data exists on abacavir apart for its fixed combination in Trizivir®.

Successful Initial Therapies

AZT+3TC plus nevirapine or efavirenz

These are good, simple combinations, which also fared well when compared to PI-combinations (006 Study, COMBINE Study, ACTG 384). It may initially cause nausea, and allergies associated with NNRTIs must be considered. Lead-in treatment with nevirapine is essential, as is monitoring for the possible CNS side effects of efavirenz. Once the first weeks have passed without complications, these combinations can often be continued for many years without major problems. Although there were no differences in toxicity in the licensing study for Combivir[®] (Eron et al. 2000), we have observed that the higher 300 mg zidovudine dose is too high for some patients and may lead to anemia. In such cases, AZT+3TC as individual formulations can be tried, lowering the zidovudine dose to 250 mg. Zidovudine does not always have to be immediately replaced!

AZT+3TC+ABC

This is the easiest combination in terms of pill burden. Two tablets of Trizivir[®] daily are hard to beat! Not only patients with compliance problems, but also those with a long list of co-medications and a high potential for drug interactions (tuberculosis and MAC therapy, warfarin), are well suited. The combination is usually well tolerated, although intense counselling on the hypersensitivity syndrome is necessary. Only recently, a case of Stevens-Johnson syndrome has been described (Bossi et al. 2002). With respect to the zidovudine dose, the same applies for Trizivir[®] as for Combivir[®] – it may be too high for some patients.

One disadvantage to this regimen is that it does not seem to be as virologically potent as other combinations. In the CNAAB3005 Study, AZT+3TC+ABC was tested double-blind against AZT+3TC+indinavir. Although after one year the same number of patients had reached < 400 copies/ml, closer inspection reveals an importance difference. In patients with

> 100,000 copies/ml at baseline, only 31 % versus 45 % reached a viral load below 50 copies/ml. However, the study was randomized double-blind – and all patients took a total of 16 pills a day, distributed over three dosings. As a result, the positive effect of improved compliance with Trizivir® did not apply (Staszewski et al. 2001). In CN3014, an open-label, randomized study, the inferiority of the abacavir arm was not nearly as impressive (Vibhagool et al. 2001). Nevertheless, we generally choose not to use this combination as an initial regimen in cases with a high viral load and significant immunosuppression, apart from the exceptions mentioned above. Some clinicians reject this combination completely – they are supported by newer data from ACTG A5095 which compared AZT+3TC+abacavir with AZT+3TC+efavirenz and AZT+3TC+abacavir+efavirenz. The study found that virological failure was significantly more likely in the AZT+3TC+abacavir arm.

AZT+ddI plus nevirapine or efavirenz

In combination with AZT+ddI, more data is available on nevirapine than on efavirenz. AZT+ddI+nevirapine is probably the oldest HAART combination. It was already tested between 1993 and 1996, in the ACTG 193A Study. Here it proved superior in advanced patients (<50 CD4+ cells) as compared to mono- and dual therapies with regard to both survival and disease progression (although not significantly for the latter; Henry et al. 1998). AZT+ddI+nevirapine was also investigated in the INCAS Trial and ACTG 241 (Raboud et al. 1999, D'Aquila et al. 1996). In the INCAS Trial, AZT+ddI+nevirapine decreased viral load below the level of detection of 20 copies after one year in 51 % of patients, compared to 12 % on AZT+ddI, and 0 % on AZT+nevirapine. Rates of clinical progression were 12 %, 25 % and 23 %, respectively (not significant, $p=0.08$). In ACTG 241 (AZT+ddI+nevirapine versus AZT+ddI alone), although no trend in favor of the triple combination in treatment-

experienced patients was demonstrated, the study did not have sufficient power to detect such differences.

d4T+3TC plus nevirapine or efavirenz

The nuke backbone of d4T+3TC is useful if problems with hematopoiesis (anemia, leukopenia or thrombocytopenia) are present or are to be expected. This applies to patients receiving chemotherapy or ganciclovir. The possibility of polyneuropathy must be considered with d4T. Antiviral efficacy should be high; in the Australian OzCombo2 Study, d4T+3TC in combination with nevirapine was as effective as d4T+ddI or AZT+3TC (French et al. 2002).

d4T+ddI plus nevirapine or efavirenz

This will probably become an important once-daily combination after licensing of d4T XR and nevirapine for once-daily dosing. The Spanish Scan Study showed that the combination of d4T+ddI+nevirapine was also effective if didanosine and nevirapine were given once daily (Garcia et al. 2000). In the Australian OzCombo2 Study, d4T+ddI in combination with nevirapine was as effective as d4T+3TC or AZT+3TC (French et al. 2002).

Two nukes plus saquinavir/ritonavir

The combination of AZT+ddC+saquinavir-HGC was the first PI-combination for which a survival benefit was shown in a randomized study, in fact the largest randomized HIV study to date (Stellbrink et al. 2002). Today, however, saquinavir is generally given in its boosted form and with other NRTIs. Without ritonavir, the pill burden would be too high, the bioavailability of saquinavir being too low. The soft gel capsules provide improved efficacy (Mitsuyu 1998), but require a large number of pills. The boosted combination of 1000 mg saquinavir and 100 mg ritonavir, both twice daily, has recently been licensed.

Two nukes plus lopinavir/ritonavir (LPV/r)

This combination has become fairly popular, although convincing data for its preferred use as an initial regimen is still lacking. In the first larger study, viral load in around 80 % of patients on lopinavir/ritonavir plus d4T+3TC was below 50 copies/ml after one year (Murphy et al. 2001). This result should also be attainable with other combinations. In combination with d4T+3TC, lopinavir/ritonavir does, however, seem to be superior to nelfinavir, as was shown in a randomized, double-blind study. At week 48, 67 % versus 52 % of patients had a viral load below 50 copies/ml (Walmsley et al. 2002). Whether this drug is really more effective than other boosted PIs may be questioned. Data from the MaxCmin2 Trial will hopefully clarify the issue.

Two nukes plus indinavir/ritonavir

Indinavir-based HAART regimens are among the regimens which have been most extensively tested. Efficacy has been proven in numerous studies. There is at least one study with clinical endpoints (Hammer et al. 1997). In the double-blind, randomized AVANTI2 Study, 46 % of patients on AZT+3TC+indinavir had < 20 copies/ml after 52 weeks, compared to only 4 % on AZT+3TC (AVANTI2 2000). Even when more extensive data exists on unboosted use of indinavir in treatment-naïve (or barely pre-treated) patients (AVANTI2, STARTI+II, OzCombo1, Merck 035, 006, ACTG 320, CNA3005), indinavir should no longer be given without boosting. Two boosted combinations (800/100 and 400/400) have been well tested. In an uncontrolled study, the number of patients with < 500 copies/ml in the ITT analysis was 73 % after 72 weeks (Lichterfeld et al. 2002). The tolerability of indinavir/ritonavir combinations can be problematic. In studies such as BEST or NICE, switching from indinavir to indinavir/ritonavir led to a slight increase in both side effects and drop-out rate (Gatell et al. 2000, Harley et al. 2001, Shulman et

al. 2002). Tolerability is probably lower than for saquinavir/ritonavir.

Which nukes should be added to indinavir/ritonavir? It probably doesn't matter. In the Start II Study, a trend was shown in favor of d4T+ddI versus AZT+3TC (Eron et al. 2000). In STARTI, d4T+3TC and AZT+3TC were about equivalent (Squires et al. 2000). A further Australian study also found no differences between d4T+3TC, AZT+3TC and d4T+ddI (Carr et al. 2000).

Two nukes plus nelfinavir

The virological effect of nelfinavir combinations has been well proven, especially when used with the nuke backbone of AZT+3TC. In the double-blind Agouron 511 licensing study, 55 % of nelfinavir patients had a viral load below 50 copies/ml after 24 weeks, versus 4 % in the placebo arm (Saag et al. 2001). In AVANTI-3, another double-blind, randomized study, the effect of nelfinavir was approximately one log above placebo (Gartland 2001). In the COMBINE Study, nelfinavir appeared as effective as nevirapine, even if a trend could be demonstrated in favor of nevirapine (Podczamzer et al. 2002). Nelfinavir, however, does not seem to be as effective as boosted PIs. In a direct comparison with lopinavir/r on a backbone of d4T+3TC, it performed less well than lopinavir/r (Walmsley et al. 2002). Nelfinavir-containing combinations have a high pill burden and are associated with unpleasant diarrhea. They are therefore now being used less frequently.

Future Combinations

Future combinations need to be more effective, simple and tolerable. However, one cannot always wait for new drugs to be developed! As a result, there are three approaches currently being investigated with available drugs: combinations that require dosing only once-daily; combinations without any nucleoside analogs; and combinations using more than three active drugs. These approaches will presumably lead to important changes in antiretroviral therapies over the next two years.

The nuke-free zone

Increasing knowledge of mitochondrial toxicity has slowly led to a change in direction in antiretroviral therapy. Whereas until recently nucleoside analogs were still considered essential components, this dogma has now become less absolute. These new considerations are supported by observations such as those from a long-term study in which patients receiving saquinavir/ritonavir had their treatment intensified either with nucleoside analogs or not (Cohen et al. 2002). The five-year data was clear. There was significantly less lipodystrophy in patients on PIs only – even if this is an unusual type of ART. In line with current opinion, lipodystrophy thus seems to be caused above all by the combination of nukes and PIs. PI-only combinations (eg. saquinavir+lopinavir/r) are likely to be the subject of studies in the near future. To date, results from studies on combinations of a PI with abacavir, the nucleoside analog that probably has the least mitochondrial toxicity, have not been particularly impressive (McMahon et al. 2001).

The multi-center EASIER Trial aims to establish whether nucleoside analogs are needed at all: patients receive indinavir/ritonavir and efavirenz, and are randomized for d4T or not. First results in 74 patients show comparable results in surrogate markers; d4T provided no additional effect (Stek et al. 2002). In the BIKS Study, patients (some with treatment experience) received a nuke-free combination of lopinavir/r and efavirenz (Allavena et al. 2002); preliminary data also indicates that such an approach may prove successful.

Nevertheless, as yet nuke-free therapies cannot be recommended, at least not for initial therapy, but they seem certain to become more important in the future (Joly et al. 2002).

Once daily

Currently only four drugs are licensed for once-daily dosing: didanosine, efavirenz, lamivudine, and tenofovir. Further candidates among the nucleoside analogs include stavudine, which

will soon be launched as an extended release capsule, and abacavir.

Nevirapine, too, seems to have favorable pharmacokinetics (Van Heeswijk et al. 2000), and it has already been used in several studies such as SCAN, VIRGO or Atlantic at a once-daily dose of 400 mg (Raffi et al. 2000, Felipe et al. 2000). If data from the 2NN Study, which is expected mid-2003, does not show conflicting results, licensing for a once-daily dosage of nevirapine is probable in the near future.

What about the PIs? Mainly boosted once-daily PI-combinations have been tested (the nucleoside analogs in these combinations were still given twice daily). A 1600 mg dose of saquinavir plus 100 mg ritonavir seems to be effective (Kilby et al. 2000, Cardiello et al. 2002). The same applies to a 1200 mg dose of indinavir plus 400 mg ritonavir (Hugen et al. 2000). Amprenavir and lopinavir/r are also possible candidates. In the M99-056 Study, treatment-naïve patients were randomized, on a backbone of d4T+3TC, to receive lopinavir/r either once-daily (1 x 6 tablets) or at the usual twice-daily dose (2 x 3 tablets). At 48 weeks, no differences in either treatment success or side effects could be shown (Eron et al. 2002). All these boosted combinations have in common, however, a high pill burden of between 6 and 9 tablets or capsules. Such treatment regimens are therefore unlikely to achieve great relevance, especially with a once-daily PI such as atazanavir soon to become available.

Thus, over the next 12-24 months a number of new options for once-daily regimens will become available. First studies in treatment-naïve patients are showing promising results (see table below).

Once-daily regimens will not only be used as initial therapy; numerous studies are currently investigating switching to such regimens. First data shows that this, too, seems effective. In a Spanish study, patients on stable HAART (>6 months below 200 copies/ml) were randomized to continue their BID-regimen or switch to a once-daily regimen of ddI+TFV+NVP. Among

the 56 patients who have reached Week 24, only one patient in each of the two groups had an increase in viral load (Negredo et al. 2002).

Table 5.4: Once-daily studies in treatment-naïve patients

	n	Combination	Percentage < 50 copies/ml
Molina 2000	40	ddl+EFV+ emtricitabine	93 % after 24 weeks
Mole 2001	10	ddl+3TC+ IDV 1200/RTV 400	80 % after 12 weeks
Maggiolo 2001	75	ddl+3TC+EFV	77 % after 48 weeks
Skowron 2002	11	ddl+3TC+EFV+AFV	91 % after 48 weeks
Rosenbach 2002	25	ABC+3TC+APV 1200/RTV 300	Pending

In our experience, a far greater improvement in adherence is achieved when changing from three to two doses daily rather than from two to one. A recently published meta-analysis showed that compliance with once-daily dosing is better than three or four times daily dosing; the difference to twice-daily dosing was not significant (Claxton et al. 2001).

Patients will not be interested in these studies; many, perhaps even most, will wish to receive a once-daily regimen. This will change the practice of antiretroviral therapy.

Intensifying therapy with 4-5 drugs

The widespread consensus that exists for the use of triple combinations as initial therapy was recently reinforced in a meta-analysis (Jordan et al. 2002) of 58 randomized clinical studies which showed the relative risk for disease progression to be approximately 0.6 compared to dual therapy.

However, some clinicians speculate whether more intensive approaches could be useful in some patients. Rapid development of resistance, which is especially likely in patients with a high viral load, is a growing concern. A number of physicians have already started to treat initially with four or five drugs, and then to simplify the regimen to a triple combination once the

viral load has dropped below the level of detection after several months.

This mainly theoretical concept has not been thoroughly validated. There are first indications from large randomized studies, such as ACTG 384 or CLASS, that certain quadruple therapies, for example, are no more potent than triple therapies (Shafer et al. 2002, Bartlett et al. 2002). In contrast, the randomized ACTG 388 Study did show a difference: 517 patients with relatively advanced HIV infection (< 200 CD4+ cells/ μ l or a high viral load) were randomized to three different regimens on a backbone of two nukes – indinavir versus indinavir+efavirenz versus the double-PI-combination indinavir+nelfinavir. The most striking result was the superior performance in the indinavir+efavirenz arm. This study is one of the first of its kind to demonstrate that a quadruple combination does provide increased efficacy. The quadruple arm with both PIs, however, was not as successful, due mainly to increased side effects rather than to the development of resistance (Fischl et al. 2002).

However, side effects during intensified regimens in treatment-naïve patients are a cause for concern. Patients may well be discouraged by the high pill burden and an increased rate of side effects. Whether, in which patients, and with which drugs such intensive treatment would be justified remains unclear.

Nevertheless, this concept can be discussed with well-informed and compliant patients. Especially in severely immunocompromised patients who have just recovered from their first AIDS-defining disease and are in need of viral suppression as quickly and successfully as possible, intensive initial treatment can be considered. In our experience, even complicated therapies become relatively tolerable when patient and physician know that a treatment regimen will be significantly reduced after a few weeks. A good combination in our experience is AZT+3TC+ABC plus a boosted PI, such as lopinavir/r.

Problems with Initial Therapies

Combinations generally considered suboptimal include all forms of mono- and dual therapy, especially two nucleoside analogs. Even one nucleoside analog plus one NNRTI is unfavorable, as the INCAS Trial has shown (Montaner et al. 1998). In addition, several situations, outlined below, should be avoided.

Problem: Combination of "D-drugs"

The two thymidine analogs AZT+d4T should not be combined within a triple regimen, as they have antagonistic effects; this was recently demonstrated in vivo (Havlir et al. 2000, Pollard et al. 2002). The same holds for the combination of the two cytidine analogs 3TC+ddC. The nukes ddI+ddC and d4T+ddC should also be avoided in combination because of the increased rate of side effects (polyneuropathy). At least one study, the French MIKADO Trial, has shown that polyneuropathy due to d4T+ddC in immunologically stable patients is not as frequent as anticipated for this combination (Katlama et al. 1998). Although the combination of d4T+ddI is currently still recommended, renewed appraisal is warranted in view of increasing evidence of mitochondrial toxicity. There will have to be new discussions in coming years on this issue. Some clinicians now reject this combination for initial therapy. Besides lipoatrophy, polyneuropathy, lactic acidosis and pancreatitis, recent reports of progressive neuromuscular weakness also give rise to concern.

Problem: Unsuitable individual drugs

The unboosted HGC formulation of saquinavir (Invirase[®]) is now unsuitable, as too low plasma levels are attained. The Euro-SIDA Study demonstrated that patients on saquinavir-HGC had a significantly higher risk for progression to AIDS (RR 1.30) compared to indinavir (Kirk et al. 2001). Similarly, the randomized Master-1 Study showed saquinavir-HGC to be significantly weaker than indinavir (Carosi et al. 2001). How-

ever, the SV14604 Study with saquinavir-HGC is to date the largest HAART study worldwide with clinical endpoints. It demonstrated an approximately 50 % reduction of AIDS with AZT+ddC+SQV-HGC compared to AZT+ddC (Stellbrink et al. 2000). Ritonavir is also unsuitable as an individual drug, as it is so badly tolerated at its full dose. Saquinavir-SGC should also not be considered since the pill burden is too high; no patient today can be expected to take 3 x 6 capsules daily. Amprenavir (for which there are relatively good data: Goodgame et al. 2000), delavirdine and tenofovir should also be excluded from initial regimens as they have not been licensed for this purpose.

Problem: Starting abacavir plus NNRTIs simultaneously

A new abacavir-containing combination should not include a new NNRTI. Both can cause allergies, which are hardly distinguishable from one another. In the case of abacavir, even a suspected allergy rules out re-exposure, and this important drug may be “lost” unnecessarily for all future combinations. Thus, if abacavir and NNRTIs are to be taken together in a new combination, initiations of treatment with the two drugs should be spaced at least 4-6 weeks apart.

Problem: Combination of NNRTIs

Too little is known concerning the combination of two NNRTIs. No sound argument exists for why two NNRTIs should be given at the same time. All NNRTIs act non-competitively at the same site, and furthermore all can cause a rash. Efavirenz levels seem to be lowered significantly in combination with nevirapine (Veldkamp et al. 2001). This is probably also true for delavirdine (Harris 2000). In a first pilot study, however, this combination appears to be effective. In the framework of a slightly confusing design, both treatment-experienced and treatment-naïve patients received a combination of NVP 400 mg + EFV 600 mg + ddI 400 mg, all once daily. Most patients were able to reach a viral load below the level of detection (Maggiolo et al. 2000). In another study, this combination also proved quite successful (Jordan et al. 2000).

Nevertheless, although to date such results have been limited to poster presentations, first data from the 2NN Study (The Double Non-Nucleoside Study) clearly showed that the combination of efavirenz and nevirapine should be avoided.

Problem: Simplifying successful HAART to two drugs

Can triple therapy be reduced to two or even one drug? Since 1998 the answer has been negative. At that time, three randomized studies were published disproving the theory that HIV infection can be treated, similarly to leukemia, by an intensive induction therapy followed by less toxic maintenance therapy.

In the French Trilège Trial, 279 patients on sufficient HAART were randomized to three study arms of different intensities (Pialoux et al. 1998, Flander et al. 2002). At 18 months, 83 patients had a viral load > 500 copies/ml – 10 on AZT+3TC+IDV, 46 on AZT+3TC and 27 on AZT+IDV. However, patients on temporary dual therapy did not apparently develop any major resistance (Deschamps et al. 2000). A further 18 months after randomization, no differences could be shown. A proportion of the patients in the dual therapy groups had been switched back to the original regimen.

What about starting with quadruple therapy and simplifying to dual therapy? This approach also failed. In the ADAM Trial (Reijers et al. 1998), patients who had been treated with d4T+3TC plus saquinavir+nelfinavir for several months either discontinued the nucleoside analogs or continued with the medication. The interim analysis caused the study to be brought to a halt: after 12 weeks viral load had become detectable in 9/14 (64 %) of the “simplifiers” versus 1/11 (9 %) of those continuing the initial regimen!

The third study, which finally destroyed all hopes of maintenance therapy, was ACTG 343, which recruited 316 patients with a viral load of < 200 copies/ml for more than two years. Patients either continued to receive AZT+3TC+IDV or changed to a simplified regimen of AZT+3TC or indinavir. The rate of treatment failure (viral load > 200 copies/ml) was 23 % in both

maintenance arms versus only 4 % in patients with continued therapy (Havlir et al. 1998).

As attractive as the approach would have been, it seems doomed – at least in patients with a high viral load at baseline.

The case is not yet closed, however, for double-PI combinations. The successes in salvage therapy (see the corresponding chapter) have shown that such treatment could perhaps be effective after all. In the Prometheus Study, PI- and d4T-naïve (partly also completely treatment-naïve) patients were randomized to a regimen of saquinavir/ritonavir plus/minus d4T. After 48 weeks, 88 % versus 91 % of patients in the on-treatment analysis had a viral load of < 400 copies/ml. However, in patients with a high viral load, the double-PI strategy proved precarious (Gisolf et al. 2000).

Problem: Starting gradually

All drugs should be started simultaneously. A number of studies have investigated whether the number of drugs should be slowly increased. At least since 1996 – the era of mono- and dual therapy – such strategies should be obsolete. In the Merck 035 Study, highly significant differences were shown between patients who had received three drugs immediately and those who were started on only two drugs (Gulick et al. 1998). The CNA3003 Study (Ait-Khaled 2002) provides a further example: 173 treatment-naïve patients were randomized double-blind to a combination of AZT+3TC+ABC versus AZT+3TC. At week 16, patients from the dual therapy arm could switch open-label to AZT+3TC+ABC or add further antiretroviral drugs if the viral load was > 400 copies/ml. At week 16, viral load was below 400 copies/ml in 10 % in the triple therapy arm versus 62 % in the dual therapy arm. More importantly, in the dual therapy arm, 37 (versus 3) patients had developed the M184V mutation. Although abacavir remained effective in most cases where it were added and TAMs were the exception, this example shows how quickly resistance can develop. Thus, initiating

triple therapy only gradually, as is sometimes practiced due to concern over too many side effects, is wrong and dangerous.

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6. When to Change HAART

Christian Hoffmann

HAART is changed for three main reasons:

1. Virological treatment failure *or*
2. Acute side effects *or*
3. Long-term toxicity (or concern about this)

Changes in antiretroviral therapy are very common, especially within the first one to two years. Treatment requires modification in approximately every second patient within the first year. In an English cohort, 44 % of patients had modified their regimen after 14 months (Mocroft et al. 2001); in a German study, 53 % of patients had changed drugs after only one year, mostly due to side effects (Fätkenheuer et al. 2001).

Virological Treatment Failure

Every change in treatment due to virological failure requires experience and a certain degree of finesse. The modification must be carefully explained to the often sceptical patient ("Shouldn't I save other drugs for later?"). HAART should be rapidly changed in the case of insufficient viral suppression and/or after an increase in plasma viremia, as suboptimal therapy always carries the risk of development of new resistance mutations, which may eliminate future treatment options via cross-resistance. In the case of clear virological failure, action must be taken without delay – the longer one waits, the more difficult things become! Insufficient viral suppression means a viral load > 50 copies/ml. Some clinicians, however, tolerate values up to 500 or even 1,000 copies/ml. In patients with good options for subsequent regimens and good compliance, we consider this unwise (with the few exceptions described below). The patient's frequent argument "But I'm fine!" has to be ignored.

In cases of clinical treatment failure (disease progression) or immunological failure (stagnation or decrease in CD4+ T-lymphocyte level) in which the viral load is below 50 copies/ml, the success of a change in therapy is uncertain; HAART alone can hardly improve such situations since it cannot do more than inhibit viral replication.

Several questions need to be addressed when considering the needs of the individual patient:

a) What are the reasons for the (increased or still increased) measurable viral load?

A viral load > 50 copies/ml does not necessarily mean that resistance mutations have developed. It may also indicate insufficient plasma levels (monitor if possible!). Compliance is important, too. The possible difficulties of the regimen should be openly addressed: Is it the number of pills? Do restrictions in food intake cause problems? Would once-daily treatment be better? Are there other reasons, such as depression? The risks of resistance developing due to non-compliance should be reiterated. If the viral load does not decrease below the level of detection or if it rebounds under the initial therapy in a compliant patient (monitor blips at short intervals!), treatment should be changed as soon as possible.

b) How vulnerable is the present combination – how quickly should action be taken?

NNRTI regimens are extremely sensitive. There is danger of cross-resistance, and a prompt change in therapy is vital. Rapid development of resistance can also be expected with lamivudine. A PI-containing regimen without an NNRTI may allow a little more time. But the credo still applies: The higher the viral load at the time of modification, the lower the chances of success. One should not wait too long.

c) What options does the patient have, and what are the consequences of the change in therapy?

The more options that are still available, the sooner they should be used. Therapy can often be intensified quite easily (e.g.

adding abacavir plus an NNRTI), and in such cases the decision to change the regimen is less difficult.

On the other hand, it may also make sense to continue therapy in a patient taking three nucleoside analogs. While this may lead to NRTI-resistance, it allows sparing of NNRTIs and PIs.

In other cases, intensification of therapy may not be feasible. A patient on treatment with drugs from all three drug classes and who had extensive pre-treatment usually has few options left, and the goal of achieving a viral load below detection level may have to be abandoned (see also "Salvage therapy").

Change Due to Side Effects

Not every side effect requires immediate modification of the treatment regimen. One should always remember that the number of available drugs is limited. Gastrointestinal side effects, as may occur during the first weeks, are not dangerous and often improve spontaneously or can be treated symptomatically. The same is true for other side effects (see the chapter on "Management of Side Effects"). However, certain side effects almost always require discontinuation of HAART. These include:

- Severe diarrhea, which persists despite loperamide even after several weeks (usually due to nelfinavir, saquinavir or ritonavir)
- Severe nausea, which persists despite metoclopramide, requires continuous treatment or leads to weight loss (usually due to zidovudine and didanosine)
- Severe anemia (zidovudine)
- Pancreatitis (didanosine, also possibly lopinavir/r)
- Lactic acidosis (most often d4T+ddI, less frequently other nucleoside analogs)
- Severe allergies with involvement of mucous membranes, fever (abacavir, NNRTIs, amprenavir)

- Renal failure, nephrolithiasis or recurring renal colic (indinavir)
- Hepatotoxicity with transaminases > 100 U/l (nevirapine, ritonavir)

Viral Load below the Level of Detection – Concern Over Lipodystrophy

Over the past few years, many clinicians have started changing PI-containing combinations replacing PIs with NNRTIs or a third nucleoside analog (review in: Murphy and Smith 2002). Their decision was due to concern about metabolic problems, which are predominantly attributed to PIs, or the wish to simplify therapy and improve compliance. Many uncontrolled "switch studies" have flooded conferences in the last two years. Some randomized studies are summarized in Table 6.1.

The overall impression is that switching from PI-containing to NNRTI-containing combinations is immunologically and virologically safe. Quality of life is generally improved. Side effects, however, have to be taken into consideration: nevirapine causes a rash or hepatotoxicity in 5-10 % of patients, and efavirenz causes CNS side effects. Lipid levels are significantly improved by nevirapine, whereas the effect of efavirenz is much less pronounced. However, whether lipodystrophy actually improves is still unclear. Changing to three nucleoside analogs may involve an increased risk of virological failure, especially in treatment-experienced patients or in the presence of NRTI resistance mutations.

Table 6.1: Randomized studies on switch from PIs to other drugs *

Source	n	Switch to	When	Virologically	Effect of switching
Barreiro 2000	135	NVP	24	Switch advantageous	Lipids unchanged, LD improved
Martinez 2001	93	EFV		Trend against switch	Lipids partly improved, LD improved, LA worse
Becker 2001	346	EFV	48	Switch advantageous	Lipids unchanged, LD improved
Carr 2001	81	ABC+NVP + ADF+HU	24	n.s.	Lipids improved, LD improved, LA worse
Clumeck 2001	211	ABC	24	Switch advantageous	Lipids improved
Ruiz 2001	106	NVP	48	n.s.	Lipids improved, LD unchanged
Negredo 2002	77	NVP or EFV	48	n.s.	Lipids only improved on NVP, LD unchanged
Opravit 2002	163	ABC	84	Trend against switch	Lipids improved
Fisac 2002	92	NVP or EFV or ABC	48	NVP/EFV similar, trend against abacavir	Lipids improved, esp. in NVP arm, LD unchanged

* In all studies randomization was against continuation of PIs. All had open-label design. At the time of switch, all patients had been on PIs for several months with viral loads below the level of detection. In all studies quality of life (if tested) was improved in the switch groups.

LD = lipodystrophy, LA = lipoatrophy, n.s. = not significant

7. How to Change HAART

Christian Hoffmann

The approach to changing a therapy which is successful but intolerable due to side effects is usually straightforward. The suspected drug should be replaced with another drug of the same class. Difficulties arise if alternate drugs are contraindicated because of potential toxicities or if resistance mutations against these drugs are suspected. In some cases, the occurrence of side effects can also be used as an opportunity to simplify therapy or reduce the pill burden.

When changing therapy due to virological treatment failure, the same conditions apply as when initiating therapy. Compliance, dosing issues, concurrent diseases, comedications and drug interactions must be considered. Treatment history and possibly existing resistance mutations are also important. The basic principles: The faster the change, the better; and: The more drugs that are changed, the higher the likelihood of success for the new regimen. Although desirable before any change in treatment, resistance tests are not always practical.

Table 7.1: Switching in the presence of known resistance mutations for individual drugs (modified from Soriano 2000)

Previous drug	Resistance mutation	New drug
Nelfinavir	D30N	Other PIs
Nelfinavir	L90M	Not saquinavir, boost new PI, preferably lopinavir/r
Nevirapine	Y181C	Efavirenz
Nevirapine	K103N	No NNRTIs
Stavudine	none	Zidovudine
Stavudine	215, 41	Didanosine, lamivudine
Stavudine	MDR*	Didanosine

* MDR = multidrug resistance

In certain cases, the prescription of a sequence of drugs from one particular class seems feasible; this has been shown for nelfinavir, nevirapine and stavudine. The following table shows treatment possibilities in the presence of individual resistance mutations.

If the increase in viral load is modest, treatment success may be achieved even with simple changes – if one acts quickly. In the case of two nukes plus an NNRTI, for example, treatment may possibly be intensified simply by the addition of abacavir or tenofovir. In a placebo-controlled study, 41 % of patients on stable ART with a viral load between 400 and 5,000 copies/ml achieved a viral load < 400 copies/ml at 48 weeks after addition of abacavir only (Katlama et al. 2001). Such results could possibly be even better with more rigorous entry levels (for example, change of therapy not at 5,000 but already at 500 copies/ml). Addition of tenofovir to stable HAART reduced viral load by 0.62 log (Schooley et al. 2002). We have had good experience with this approach in cases with minimal increases in viral load (up to 500 copies/ml) in the absence of TAMs. However, there is as yet no controlled data concerning this issue.

In patients who have been treated exclusively with NRTIs (in particular after prolonged treatment), this strategy is generally unsuccessful. Extensive resistance mutations usually exist, so that a complete change of HAART is necessary. At least two randomized (and partly blind) studies have shown that most benefit is achieved by switching to an NNRTI plus a PI plus at least one new nucleoside analog. This has been shown for both nelfinavir plus efavirenz and indinavir plus efavirenz (Albrecht et al. 2001, Haas et al. 2001). In patients previously treated with NRTIs or NNRTIs, a PI must be used. The realm of salvage therapy is entered when a PI-regimen fails (see next chapter: "Salvage Therapy").

Table 7.2: Changing initial therapy without knowledge of resistance mutations*

Failing initial therapy	If VL	Potentially successful change
3 Nukes	50-500	2 new nukes plus TDF plus NNRTI
	>500	2 new nukes plus NNRTI (possibly plus PI)
2 Nukes + 1 NNRTI	50-500	3 nukes plus TDF plus continued NNRTI
	> 500	2 new nukes plus PI (NNRTI depending on resistance)
2 Nukes + 1 PI	50-500	Possibly new boosted PI or boost present PI
	> 500	2 new nukes plus NNRTI plus possibly TDF (plus possibly new boosted PI or boost present PI)
2 Nukes + 1 PI (boosted)	< 50	2 new nukes plus NNRTI plus possibly TDF

* Note: There is insufficient data available on all these changes. In individual cases, other modifications or simply waiting may be advisable.

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8. Salvage Therapy

Christian Hoffmann

Background

The term "salvage therapy" is ill-defined. It is currently used confusingly in both HIV medicine and oncology to refer to varying situations. Some clinicians speak of salvage only if all drug classes have failed, whereas others employ the term from second-line therapy onward. As yet no consensus on the definition of salvage has been reached. We define salvage as the therapeutic approach when at least one PI-containing regimen has failed.

The investigation of new salvage strategies is problematic as it is difficult to find homogeneous and sufficiently large patient study populations. Although patients with multiresistant viruses are no longer hard to find, each patient has an individual pre-treatment history, different resistance mutations and thus different prerequisites for a salvage regimen. In any one larger clinical center, more than 30 to 40 different combinations are in use. As a result, few randomized studies have been conducted. Only recently have larger trials been initiated. The OPTIMA Study (OPTions In Management with Antiretrovirals) is currently investigating different strategies, such as Mega-HAART or three-month treatment interruption, in 1,700 patients before initiation of a new HAART regimen. The results will not be available for a while, and until then, one must rely on data from uncontrolled studies, which usually describe between 20 and 100 salvage patients.

At least one important conclusion has been established by these studies: The higher the viral load on the failing PI-regimen, the worse the chances of success for the subsequent combination (Chavanet et al. 2001, Deeks et al. 1999, Hall et al. 1999, Pare-

des et al. 1999, Mocroft et al. 2001). The more time the virus has to develop resistance, the more intractable it becomes!

Furthermore, various studies have shown that usually only 30 to 50 % of patients who fail PI-regimens are able to achieve a viral load below the level of detection on a boosted combination such as ritonavir/saquinavir (Deeks et al. 1998, Fätkenheuer et al. 1999, Hall et al. 1999, Paredes et al. 1999). The responses to ritonavir/saquinavir may be slightly improved if the initial regimen contained nelfinavir (Tebas et al. 1999); this is probably due to the D30N mutation specific for nelfinavir.

The few available randomized salvage studies are shown in the following table.

Table 8.1: Randomized salvage studies *

	n	Previous therapy	Salvage regimen	Viral load success	Success
Hammer 2002	481	1-3 PIs	ABC+EFV+APV+AFV plus 2nd PI	<200 Wk 24	23 % 35 %
Gulick 2000	277	IDV, no NNRTI	RTV/SQV+DLV RTV/SQV+AFV RTV/SQV+DLV+AFV NFV+SQV+DLV NFV+SQV+AFV NFV+SQV+DLV+AFV	< 500 Wk 16	33 % 20 % 31 % 47 % 16 % 36 %
Jensen-Fangel 2001	56	1 PI, no NNRTI	NFV+2 nukes NFV+NVP+2 nukes	< 200 Wk 36	22 % 52 %
Raguin 2002	37	PIs, NNRTIs	LPV/r+APV LPV/r+APV+RTV	< 50 Wk 26	32 % 61 %

* Viral load success means viral load below the level of detection at a certain time point. All patients had extensive NRTI-experience. AFV=adefovir

The recently published ACTG 398 Study is to date the largest randomized salvage study (Hammer et al. 2002). It randomized 481 patients with a viral load > 1,000 copies/ml and extensive pre-treatment to either receive a second PI (depending on the

previous treatment) or not. Earlier observations were confirmed: Only 31 % of patients achieved a viral load < 200 copies/ml after 24 weeks. In the group receiving two PIs the rate was significantly higher (35 % versus 23 %). On the whole, the response to the salvage regimen was – until the introduction of lopinavir/r – rather modest (review in: Battegay et al. 1999).

Salvage with Lopinavir/Ritonavir (LPV/r)

The introduction of lopinavir/r (Kaletra[®]) has significantly improved salvage therapy. Even if the value of lopinavir/r may be contested in treatment-naïve patients or with regard to the disturbing occurrences of dyslipidemia, the drug remains unchallenged among all other compounds approved for salvage. The resistance barrier is high (Kempf et al. 2001), and even patients with extensive treatment may experience benefit. Lopinavir/r-containing combinations should therefore be considered after failure of the first PI. Response is often surprisingly good, and the higher the plasma levels, the better (Boffito et al. 2002). At least 5-7, if not 8 PI-mutations are necessary for failure of lopinavir/r (Kempf et al. 2001, Masquelier et al. 2002). In 70 patients with a failing PI-regimen, the decrease in viral load was an impressive 1.4 log at two weeks after simple substitution of the PI with lopinavir/r (Benson et al. 2002). A realistic example of the often astonishing salvage effect of lopinavir/r is shown in the table below.

Table 8.2: Patient example of the success of lopinavir/r in salvage therapy

Date	(HA)ART	CD4+ T cells	Viral load
Mar 93	AZT	320	N/A
Jan 95	AZT+ddC	190	N/A
May 96	AZT+3TC+SQV	97	N/A
Feb 97	d4T+3TC+IDV	198	126,500
Aug 97	d4T+3TC+NfV	165	39,500
Mar 98	d4T+ddI+SQV/RTV+HU	262	166,000
Sep 98		238	44,000
July 00	AZT+3TC+NVP+LPV/r	210	186,000

Oct 00	385	< 50
Oct 02	685	< 50

This example illustrates several phenomena: Insufficient responses to new regimens after failure of the first PI; insufficient viral suppression over two years with surprisingly stable CD4+ T cell levels; and finally a durable response to lopinavir/r – after more than four years of suboptimal PI-treatment! NNRTI hypersusceptibility may also have possibly been present in this case (see below). At the time of switch to lopinavir/r, genotypic and phenotypic resistance to various nucleoside analogs (and PIs) had developed.

Salvage with Double Boosting

A further current approach in salvage therapy is to use low ritonavir doses (as contained in Kaletra[®]) to boost not only lopinavir but also other PIs such as saquinavir, amprenavir and indinavir. In vitro data has shown that this is probably most effective with saquinavir, as there seems to be synergy between the two drugs (Molla et al. 2002). The ritonavir mini-dose in Kaletra[®] (standard dose) seems to be sufficient for 1000 mg saquinavir bid, as pharmacokinetic data shows (Stephan et al. 2002). The unfavorable pharmacokinetic interactions that have been demonstrated between amprenavir and lopinavir/r, for example (Back et al. 2002), do not seem to affect saquinavir and lopinavir/r. The former combination, however, seems to attain reasonable results with the addition of an extra ritonavir boost (200 mg) (Raguin et al. 2002).

On the other hand, a small observational study showed better responses with the combination lopinavir/r + saquinavir than with lopinavir/r + amprenavir (Zala et al. 2002). In a German study of highly treatment-experienced patients (median 9 different treatments!) who were switched for differing reasons (e.g. resistance, toxicity) to a combination of lopinavir/r + saquinavir, 19/33 patients achieved a viral load < 50 copies/ml

after 24 weeks (Staszewski et al. 2002). Some patients had interrupted therapy before starting the salvage regimen.

Mega-, Giga-HAART

Following the slogan "the more, the better", several studies have shown that different intensified treatment combinations – described also as "Mega-HAART" or "Giga"-HAART – may indeed be effective. The success of these mostly uncontrolled studies can be debated. On five- or six-drug regimens, sufficient suppression of viral load was achieved in a variable percentage of patients (22-52%; Grossman et al. 1999, Miller et al. 2000, Montaner et al. 2001, Piketty et al. 2002, Youle et al. 2002).

So, do treatment interruptions before initiation of such intensified regimens provide additional benefit? Maybe, but we just don't know. In the GIGHAART Study (Katlama et al. 2002), highly treatment-experienced patients with advanced HIV infection (< 100 CD4⁺ T-lymphocytes/ μ l, VL $> 50,000$ copies/ml) were switched after a treatment interruption of up to eight weeks to a combination of 7-8 drugs: 3-4 nucleoside analogs, hydroxyurea and 3 PIs. In the group that had undergone treatment interruption, the effects after 24 weeks were significantly better, the decrease in viral load being 0.29 versus 1.08 log. However, this promising result still needs to be confirmed.

According to some critics, all salvage studies, to put it bluntly, can only be considered as the administration of short-term, poisonous cocktails. However, many issues still need to be addressed. Mega-HAART regimens are generally not individualized. Furthermore, their success is a function of three variables: resistance, plasma levels, and adherence. The latter is always likely to be difficult with such therapy. Only well-informed and extremely compliant patients should therefore be considered for Mega-HAART regimens. Furthermore, any drug interactions are difficult to predict in this setting, and plasma levels should be measured whenever possible. Most PIs, however, may be combined with each other quite well without causing significant

interactions or toxicities (van Heeswijk et al. 2001, Eron et al. 2001).

Despite all the discussions concerning Mega- or Giga-HAART, for some patients the primary treatment goal of achieving a viral load below the detection level must be abandoned. Sometimes it may be wiser to lower the hurdle and wait for new options such as tipranavir or entry inhibitors. These patients should be monitored in larger centers where new options are available sooner and where clinicians have experience with intensified regimens. "Squandering" one single new drug at a time should be avoided; if possible two or more effective drugs should be used!

NNRTI Hypersusceptibility

Viral strains are considered hypersusceptible to certain drugs if the IC₅₀ (50 % inhibitory concentration) for the drug is lower than that of the wild-type in phenotypic resistance tests. This phenomenon, for which the biochemical correlate is still the subject of debate, occurs generally very rarely with nucleoside analogs, but quite frequently with NNRTIs, and mostly in viruses that have developed resistance mutations against nucleoside analogs.

NNRTI hypersusceptibility was first described in January 2000, when it was recognized that NNRTI-naïve patients did particularly well in salvage therapy (Whitcomb 2000). Several prospective studies have since described this phenomenon more closely (Albrecht et al. 2001, Haubrich et al. 2002, Katzenstein et al. 2002, Mellors et al. 2002). In a recently published analysis of more than 17,000 blood samples, the prevalence in NRTI-naïve patients of hypersusceptibility to delavirdine, efavirenz and nevirapine was 5 %, 9 % and 11 %, respectively. In NRTI-experienced patients, the prevalence was notably 29 %, 26 % and 21 % (Whitcomb et al. 2002). There seems to be some evidence that patients with NNRTI hypersusceptibility have better virological responses. Of 177 highly treatment-experienced (but NNRTI-naïve) patients, 29 % exhibited this type of lowered

IC50 for one or several NNRTIs (Haubrich et al. 2002). Of the 109 patients who received a new NNRTI-containing regimen, those with NNRTI hypersusceptibility had better results. The viral load was significantly lower even after 12 months (-1.2 versus -0.8 log), and the CD4+ cell count was also higher.

Even if the real significance and molecular correlate for this phenomenon are still uncertain, the consequence is clear: Patients with NRTI mutations and without NNRTI resistance should always receive an NNRTI in their new regimen.

Practical Tips for Salvage Therapy

1. First question: What previous treatment has the patient received and for how long – if this is unclear, a resistance test should be performed (no resistance test during treatment interruption!).
2. After addressing point 1, use as many new (active) drugs as possible, but be vigilant for potential side effects!
3. Don't wait too long to switch, giving the virus the opportunity to develop further resistance mutations – the higher the viral load at the time of switch, the worse the chances for success.
4. Use lopinavir/r! Also consider double boosting, preferably with saquinavir.
5. Has the patient ever taken NNRTIs? If not, it's high time! If so, and if there is NNRTI-resistance: stop NNRTIs!
6. Does the CD4+ cell count and history allow for treatment interruption before a salvage regimen?
7. Don't demand too much from the patient! Not every patient is suited for Mega- or Giga-HAART.
8. Encourage the patient! Entry inhibitors, tipranavir or TMC125 are already becoming available, and there is no such thing as "untreatable". It may often be possible to "hibernate" (wait for new drugs).
9. Don't immediately exploit a single new drug – if the patient's condition and his or her CD4+ T cell count allow it, at least wait for a second new drug.

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9. When to Stop HAART

A current review of treatment interruption

Christian Hoffmann

Hardly a topic has evoked more heated discussion in the last four years than treatment interruption. However, in the debate over possible risks or advantages, many issues are often confused, without distinguishing between

- Structured treatment interruption (STI)
- Structured intermittent treatment (SIT)
- Drug holidays
- Irregular taking of drugs, and
- Permanent discontinuation of therapy

The reasons and goals for treatment interruption may differ greatly. When discussing rationale or risks, it should be clear why treatment is being interrupted:

- Due to the wish of the patient
- To improve compliance and patient psyche (“life sentence” removed)
- To reduce long-term toxicities
- For immunological reasons
- As a salvage strategy

One should not fail to realize that most treatment interruptions presumably occur without the clinician’s knowledge. For this reason alone, treatment interruptions are an important aspect of antiretroviral therapy, whether one as a clinician approves of them or not. To categorically oppose treatment interruption means to disregard the realities of treatment. The following summarizes the main findings in recent years. This chapter is limited to patients with chronic HIV infection; (for recommen-

dations on acutely infected patients see the chapter on “Acute HIV Infection”).

What Happens to Viral Load and CD4+ T-Lymphocyte Levels during Treatment Interruptions?

Almost all patients who stop treatment experience a rebound in viral load within a few weeks, even patients with previously undetectable HIV levels over several years (Davey et al. 1999, Chun et al. 2000). Viral load usually rebounds above the level of detection within 10-20 days (Davey et al. 1999, Harrigan et al. 1999, Garcia et al. 1999). The time span to a doubling of plasma viral load is around 1.6 – 2.0 days. The viral load in compartments such as the CNS parallels changes in plasma (Garcia et al. 1999, Neumann et al. 1999, Smith et al. 2001), and this also probably applies to semen and vaginal fluid; patients must therefore be informed about the higher risk for transmitting HIV. Occasionally, an initial overshooting rebound of viral load is observed (De Jong et al. 1997, Birk et al. 2001). Only after a few weeks does the viral load settle to its initial, pre-treatment level (Hatano et al. 2000). The rebound virus evidently does not arise from latent reservoirs; other populations must exist, from which these new viruses can emerge within such a short period of time (Chun et al. 2000, Ho 2000, Imami-chi et al. 2001).

Treatment interruptions can have serious immunological consequences. CD4+ cell counts often fall within a short time to pre-treatment levels. In a study of 68 patients, the calculated time point at which the initial pre-HAART CD4+ cell count was reached was only 25 weeks (Phillips et al. 2001). The hard-earned successes of HAART therefore fade rapidly. CD4+ T cell losses vary greatly between patients but may reach 200 or 300/ μ l within a few weeks. The higher the CD4+ T cells and the faster the rise of CD4+ T cells on HAART, the more rapid the decrease (Sabin et al. 2001, Tebas et al. 2002). Age also seems to play a role – the older the patient, the more extensive the immunological deterioration is likely to be. The loss in

CD4⁺ T cells during interruptions may not be regained as quickly. In a prospective and controlled study, we saw a clear disadvantage for patients with treatment interruption. After a follow-up of 18 months, these patients had a median loss of 120 CD4⁺ T cells/ μ l compared to matched patients without treatment interruption (Jaeger et al. 2002).

The Risks: Development of Resistance, Clinical Problems

Viral resistance has to be anticipated whenever there is viral replication in the presence of suboptimal drug levels, and when resistant mutants have a selective advantage over the wild-type virus. As a result, there are concerns that resistance may develop particularly during the washout phase of medication (increasing viral replication with insufficient plasma levels) and on re-initiation of treatment (continued replication despite sufficient plasma levels).

However, in the case of single treatment interruptions, the probability of development of resistance in individual patients may not be particularly high, as the French COMET Study showed in 1999. In ten patients, no resistance developed during treatment interruptions, and after re-initiation of therapy, viral load was suppressed again without problems (Neumann et al. 1999). But, there is currently no certainty as to whether such interruptions might not eventually lead to development of resistant isolates, which merely require more time until they are able to dominate the wild-type. Mathematical models show that this risk – at least theoretically – is not low, especially if viral load rises to high levels (Dorman et al. 2000, Bonhoeffer et al. 2000). Newer studies have recently demonstrated that repeated treatment interruptions in particular bear a higher risk, especially for NNRTI- or lamivudine-resistance (Martinez-Picado et al. 2002, Metzner et al. 2002, Schweighardt et al. 2002). However, these studies lacked a control group to allow full evaluation of the risk for resistance.

The table below describes the example of a patient who was clinically well and requested a treatment interruption for several weeks. The repeated stop and start of HAART probably ultimately led to resistance in this case.

Table 9.1: Example for development of resistance due to repeated treatment interruptions *

Date	HAART/comments	CD4+ T cells	Viral load
Jun 97	AZT+3TC+SQV	288	67,000
Oct 99	HAART stopped, patient feeling well	540	< 50
Dec 99	Diagnosis of autoimmune hyperthyroidism	400	63,000
Jan 00	AZT+3TC+NVP (+ carbimazole)	260	74,000
Feb 00	Anemia (Hb 7.3 g/dl) HAART stopped again	347	1,500
Mar 00	d4T+3TC+NVP (+ carbimazole)		
Apr 00	Resistance mutations K103N, M184V	360	2,400

* During the first treatment interruption the patient developed autoimmune hyperthyroidism, the treatment of which led to severe anemia after re-initiation of HAART, so that HAART had to be interrupted again. As a result, resistance developed against NNRTIs and lamivudine.

Autoimmune phenomena in the context of treatment interruption as seen in this patient have not previously been described. The sharp increase in viral load which may occur can occasionally present as a retroviral syndrome. The symptoms are similar to acute HIV infection, with lymphadenopathy, fever, asthenia and malaise (Colven et al. 2000, Kilby et al. 2000, Zeller et al. 2001).

During treatment interruptions, the risk of AIDS seems to be low. In the Swiss Cohort, the risk for progression was not increased (Taffe et al. 2002). We observed no increased risk of AIDS after 18 months in 127 patients interrupting treatment, compared to 252 matched controls (Jaeger et al. 2002). However, most patients were immunologically stable. The lower the CD4+ T cells, the higher appears the risk; in a smaller study in

significantly immunocompromised patients, several AIDS-defining illnesses occurred (Deeks et al. 2001).

STI at the Patient's Wish, for Reduction of Toxicity

Interruption of therapy may have psychological advantages (Tuldra et al. 2001). Many patients are relieved of the burden of continuous, lifelong therapy. The wish for treatment interruption should be taken seriously. Presumably most patients expressing such a wish will interrupt sooner or later anyway; so the interruption may as well be structured!

What about side effects? Increased lipid levels (cholesterol, triglycerides) drop quite rapidly after stopping treatment (Hatano et al. 2000, Jaeger et al. 2002). However, the reduction of drug exposure during interruptions is unlikely to be so significant as to affect the cardiovascular risk profile.

Lactate and elevated liver function tests may also decrease fairly rapidly (Jaeger et al. 2002). In many patients, symptoms such as fatigue or asthenia quickly disappear. A recent widely reported study showed that mitochondrial DNA actually regenerates during treatment interruptions (Cote et al. 2002). Whether lipodystrophy improves has not yet been proven. Short treatment interruptions have not had any effect on morphological changes (Hatano et al. 2000). Resolution of lipodystrophy even after longer interruptions is by no means certain; we have a patient who was treated during seroconversion in whom a buffalo hump developed after one and a half years, which has not resolved two years after treatment interruption.

STI – for Immunological Reasons

Hardly any patient has become as famous as the acutely infected man treated in a Berlin private practice a few years ago who, with a viral load of approximately 80,000 copies/ml, began a HAART consisting of didanosine, indinavir and hydroxyurea. The virus rapidly became undetectable. After several problems – and two short treatment interruptions – HAART

was finally stopped after 176 days. Astonishingly, even without drugs, plasma viremia in this patient has remained below the level of detection for more than four years.

Although virus was still detectable in lymph nodes, thus excluding eradication, the immune system in this case – referred to as “The Berlin Patient” among experts in the field (Liszewicz et al. 1999) – was obviously capable of controlling the infection. But why? Was it the early initiation of therapy, the hydroxyurea, or the treatment interruptions?

While such strategies seem promising in acutely infected patients (see also the chapter on “Acute HIV Infection”), the case of the Berlin patient led to a series of attempts to improve HIV-specific immune responses with temporary treatment interruptions, even in chronically infected patients. According to the hypothesis of “endogenous vaccination”, the temporary viral load rebound would strengthen HIV-specific immune responses, which decline with increasing viral suppression on HAART.

Even though many immunologists postulated that this theory made no sense (in other infections, only minimal stimuli are required to generate a sufficient immune response), reports during 2000 and 2001 were encouraging. Numerous small studies, usually involving 2-6 patients, were widely discussed; each successive interruption seemed to prolong the time to viral rebound or decrease the rate of rebound, and, in parallel, there were measurable improvements in HIV-specific CD4+ or CD8+ T cell immune responses (Carcelain et al. 2000, Haslett et al. 2000, Garcia et al. 2001, Lori et al. 2000, Ortiz et al. 1999, Pappasavvas et al. 2000, Ruiz et al. 2001).

STI was finally “put to the test” in the Spanish-Swiss SSITT Study (Hirschel et al. 2002, Oxenius et al. 2002): 133 patients were monitored throughout four ten-week cycles, each of eight weeks HAART and two weeks of treatment interruption. After 40 weeks, HAART was permanently interrupted. Treatment success – defined as a viral load < 5,000 copies/ml without

HAART after week 52 – occurred in 21/99 patients. However, 5/21 patients had a low viral load even before initiation of HAART. Most importantly, none of the 32 patients with a pre-HAART viral load > 60,000 copies/ml achieved a viral load of < 5,000 copies/ml. This first large study in chronic infection clearly demonstrated that repeated STIs may lower the viral load set point only in few patients, usually those with low initial viral load. Even if anecdotal reports suggest the converse, in contrast to acute infection, improvement of HIV-specific immune response seems unlikely in the setting of chronic HIV infection. Treatment interruptions on immunological grounds alone are therefore not justified and are dangerous.

STI – in Multidrug Resistance

In most patients with multidrug resistance, treatment interruption leads to a gradual shift back to wild-type virus and loss of resistance. For this reason, resistance testing during treatment interruption is of little use since mutations disappear as early as two weeks after treatment interruption (Devereux et al. 1999).

This shift is particularly pronounced in modestly immunosuppressed patients. The time to shift is increased in more advanced stages of disease and with longer duration of treatment (Miller et al. 2000, Izopet et al. 2000). PI-mutations are the first to disappear, while NNRTI-mutations are the most protracted; NNRTIs probably impair viral fitness less than other antiretroviral drugs (Deeks et al. 2001, Birk et al. 2001). The wild-type is assumed merely to dominate the resistant mutants. After re-starting treatment, resistance mutations rapidly become detectable again (Delaugerre et al. 2001).

A small study has shown that mutations do not disappear during the rapid increase in viral load after treatment interruption, but rather during the slower increase preceding the plateau in viral load. The persistence of drug mutations during the initial viral load increase indicates that mutant strains may still replicate efficiently (Birk et al. 2001).

At least two studies to date have shown that the shift resulting from treatment interruptions can be beneficial for salvage strategies. In the Frankfurt Cohort, a shift was associated with improved response to the salvage regimen (Miller et al. 2000). In the GIGHAART Study (Katlama et al. 2002), patients who had interrupted treatment before starting a salvage regimen had a significantly greater decrease in viral load after 24 weeks (1.08 versus 0.29 log in the control group).

However, whether these effects are durable and provide benefit in the long-term remains unclear. Furthermore, in immunologically advanced patients, the risks of treatment interruption must be considered. In patients with a shift to wild-type, the viral load rises more significantly and T helper cells drop to lower levels (Deeks et al. 2001). This confirms other studies (Hawley-Foss et al. 2001) and our own experience, that even patients with multidrug resistance benefit clinically from continued treatment, although viral load may not be sufficiently suppressed (see the chapter on “Salvage”).

Multiresistant viruses seem to be less aggressive than the wild-type, at least for a while. In patients who are completely immunocompromised and in danger of opportunistic infections, strategic treatment interruptions are therefore inadvisable. On the contrary, all efforts should be made to contain the virus as far as possible.

SIT – a Strategy for the Future?

In the initial phase following treatment interruption, the viral load usually continues to be very low. Plasma viremia only reaches pre-treatment levels after about four, sometimes even six weeks. The risk for development of resistance is presumably small at lower levels of viral replication (Bonhoeffer et al. 2000). Does this indicate that ultra-short treatment interruptions could be utilized to reduce drugs, costs and long-term toxicities? In an NIH pilot study on SIT (structured intermittent treatment), 10 chronically infected patients with more than 300 CD4+ cells/ μ l and a viral load < 50 copies/ml were switched to

a combination of stavudine, lamivudine, ritonavir and indinavir (a relatively robust regimen with regard to resistance and plasma levels). This combination was administered with 7 days treatment and 7 days interruption for a period of at least 44 weeks. The astonishing result: neither viral load nor proviral DNA increased. CD4+ cells and the immune response remained unchanged, suggesting that the immune system is probably unaffected by such ultra-short breaks in treatment. A significant reduction in lipid levels occurred (Dybul et al. 2001). Some patients, however, experienced several blips (temporary increases in viral load) to > 100 copies/ml. At this time, it is impossible to predict whether this treatment strategy might result in a higher risk for resistance in the long term. A larger study has since enrolled 90 patients who will be randomized to receive either intermittent or continuous treatment. If this concept proves successful, it could fundamentally change antiretroviral treatment. Up to 50 % of drugs could be saved in patients with good viral suppression.

Another approach is currently being investigated in the USA in the SMART Study (<http://hiv.net/link.php?id=167>). 6,000 patients with > 350 CD4+ cells/ μ l are to be enrolled and randomized to two study arms, one to receive continuous therapy, the other to interrupt treatment whenever the CD4+ count is $> 350/\mu$ l. Therapy will be restarted when the CD4+ cells have dropped to $< 250/\mu$ l. The first patients were enrolled into this highly ambitious project in January 2002, and in view of its vast patient numbers, the first results cannot be expected before 2004. Success in this study would, however, fundamentally change the current approach of lifelong HAART.

Permanent Interruption

Can patients who, according to present guidelines, were started too early on HAART during the post-Vancouver euphoria stop treatment again for the time being? An observational study in 101 patients showed that this could be possible in many patients. 67 % of patients in this cohort at Johns Hopkins Univer-

sity have remained without HAART for a mean period of 74 weeks. The higher the CD4+ T cell level at initiation of therapy, the longer the possible interruption of HAART (Parish et al. 2002). The following table shows such an example.

Table 9.2: Example of permanent interruption after early initiation, numerous interruptions, so far without deterioration of CD4+ cells *

Date	HAART/Comment	CD4+ cells	Viral load
03/96	d4T+3TC (many interruptions)	330	15,000
03/97	d4T+3TC+SQV (some interruptions)	300	< 500
08/99	Long interruption (9 weeks)	380	< 50
11/99	ddl+3TC+NVP	491	110
09/00	Discontinuation	438	< 50
02/01	Still no HAART	390	250
07/02	Still no HAART	397	1,900
10/02	Still no HAART	268	800

The low viral load set point during the last years is astonishing – did the patient benefit from treatment interruptions?

(Note: Viral load was measured with several methods to exclude error. The relative CD4+ values were between 13-15% for the whole period)

However, no information currently exists regarding the advantages or disadvantages of treatment interruption in such patients. The decision to continue or interrupt treatment can be made only on a case by case basis.

Practical Tips for Treatment Interruptions

- Don't try to convince patients to interrupt therapy – a clear risk/benefit analysis is currently not possible!
- Those who have no problems with HAART should not interrupt therapy – STIs for immunological reasons are not meaningful in chronically infected patients.
- The patient's wish should be respected – information should be provided on clinical (retroviral syndrome), immunological (loss of CD4+ cells) and virological (resistance) consequences.
- Patients must be aware that the risk of infection is increased – even after long and complete viral suppression, viral load returns to initial levels after 4-6 weeks without HAART.
- CD4+ cells and viral load should be monitored at least monthly during interruptions.
- Risk of resistance is possibly higher with NNRTIs (choose robust regimens and stop NNRTIs one to two days earlier if possible – consider half-life of the drugs).
- Avoid interruptions in severely immunocompromised patients – benefits in salvage has not yet been proven.
- Resistance testing during treatment interruptions is pointless – it would only measure the wild-type!

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10. Monitoring

Christian Hoffmann

Which parameters should be included in routine laboratory monitoring in HIV infection? What can be expected from the results? This section deals with viral load, CD4+ cells, routine checks, and plasma levels. Resistance tests are the subject of a separate chapter (“HIV Resistance Testing”).

Viral Load

Viral load is the amount of viral copies in the blood. Alongside CD4+ cell count, viral load has become the most important surrogate marker for HIV infection (Hughes et al. 1997, Mellors et al. 1997, Lyles et al. 2000, Ghani et al. 2001), providing both valuable information on the indication for antiretroviral therapy and the critical value that determines therapy success. Other surrogate markers used frequently in the past, such as p24, neopterin or β_2 -microglobulin, are now obsolete. Viral load assays measure the amount of HIV-RNA (viral genetic material), which correlates directly with the number of viruses. The units are viral copies/ml (or genome equivalents). A change of one or more log refers to the change in viral load by one or more decimal powers.

Number of copies	Log ₁₀
10	1.0
50	1.7
100	2.0
500	2.7
1000	3.0
10000	4.0
50000	4.7
100000	5.0
1000000	6.0

Assessment

The higher the viral load, the higher the risk for a decrease in CD4+ cells, with subsequent disease progression or occurrence of AIDS-related illnesses (Mellors et al. 1997, Lyles et al. 2000). A viral load $> 100,000$ copies/ml (5.0 log) is generally considered to be high, a value $< 10,000$ copies/ml to be low. These thresholds are not absolute and can only provide points of reference.

The effects of plasma viremia on immune status can vary greatly between individuals. There are some patients whose CD4+ cells remain stable for relatively long periods despite high viral load, while others experience a rapid drop despite relatively low levels of viral load. Viral load is probably generally lower in women than in men. In a meta-analysis, the difference was 41 % or 0.23 log (95 % confidence interval 0.16-0.31 log) (Napravnik et al. 2002). The reason for this is unclear. Whether this phenomenon impacts the indication for treatment is still the subject of discussion.

Methods

Three methods or assays are currently used to measure viral load: Reverse Transcription Polymerase Chain Reaction (RT-PCR); branched-chain DNA (b-DNA); and Nucleic Acid Sequence-Based Amplification (NASBA). They differ both in levels of detection and in the linear range within which measurement is reliable or reproducible (see table below). In all methods, the minute amount of viral RNA must first be amplified to enable measurement. In the case of PCR and NASBA, the viral RNA is transformed in several enzymatic steps and then amplified to measurable amounts. B-DNA does not require this enzymatic step; signal amplification occurs via binding of branched DNA fragments to viral RNA.

Although intra-assay variability is fairly good for all three methods and one can expect reproducible values, methodological variations must be considered when interpreting the results. Differences of less than 0.3-0.5 log are not considered signifi-

cant. A decrease from 4.3 to 3.9 log, for example (corresponding to a decrease from ca. 20,000 to 8,000 viral copies/ml), does not necessarily signify a drop in viral load. The same holds for increases in viral load. Up to threefold changes can therefore be irrelevant! Patients who, after hearing mere numbers, frequently worry unnecessarily or become falsely optimistic should be made aware of this.

Table 10.1: Methods of measurement, including test version, linear range and level of detection should be clearly indicated for the clinician on every test result

Company	Roche/Abbott	Bayer/Chiron	Organon
Method	RT-PCR	b-DNA	Nuclisens HIV-1 QT
Linear range of assay	400 – 750,000 ultrasensitive: 50 – 75,000	100 – 500,000	40 – 10,000,000
Comparability	Values ca. 2 x higher than b-DNA (version 2.0 and 3.0)	Values ca. 50 % of PCR (version 2.0 and 3.0)	Values approx. like PCR
Advantages	Less false positive results than b-DNA	Equally good for all subtypes (A-G), technically relatively simple	Equally good for all subtypes, large linear range

Considerable differences exist between the three methods (Coste et al. 1996), and to change from one method to another is therefore generally not advisable. The results obtained by b-DNA are usually lower than PCR by a factor of 2. Different subtypes are also detected with varying success according to the method employed (Parekh et al. 1999); one should be particularly cautious in patients from Africa and Asia with non-B subtypes, for example, in whom the viral load at first presentation can be unexpectedly low. In such cases, use of a different assay may actually be indicated. However, newer versions with improved primers are probably superior in measuring even unusual HIV subtypes with adequate sensitivity. All assays have a linear dynamic range, outside of which precise numbers are not

so reliable. There are two tests for PCR, the standard and the ultrasensitive assay. The linear range of the ultrasensitive assay ends at 75,000 copies/ml, and thus this test should only be used if low viral loads are to be expected.

The following rule applies: one method, one laboratory! The laboratory should be experienced and routinely perform a sufficiently large number of tests. Measurement should take place as soon as possible after blood withdrawal, and correct collection and shipping of centrifuged plasma is also important (contact the laboratory ahead of time on these issues).

Influencing factors

Apart from methodological variability, a host of other factors may influence levels of viral load. These include vaccinations and concurrent infections. During active opportunistic infections, viral load is often particularly high. One study showed a 5- to 160-fold elevated viral load during active tuberculosis (Goletti et al. 1996). In these situations, determining viral load does not make much sense. Following immunizations, for instance for influenza (O'Brien et al. 1995) or pneumococcus (Farber et al. 1996), viral load may be elevated transiently (Kolber et al. 2002). As the peak in viral load occurs one to three weeks after immunization, routine measurements of viral load should be avoided within four weeks of immunization.

Viral kinetics on HAART

The introduction of viral load measurement in 1996-1997 fundamentally changed HIV therapy. The breakthrough studies by David Ho and his group showed that HIV infection has significant in vivo dynamics (Ho et al. 1995, Perelson et al. 1996). The changes in viral load on antiretroviral therapy clearly reflect the dynamics of the process of viral production and elimination. The concentration of HIV-1 in plasma is usually reduced by 99% as early as two weeks after the initiation of HAART (Perelson et al. 1997). The decrease in viral load follows biphasic kinetics. In the first phase, i.e. within the first

three to six weeks, an extremely rapid drop occurs, followed by a longer phase during which viral load only gradually further decreases (Wu et al. 1999).

The higher the viral load at initiation of therapy, the longer it takes to drop below the level of detection. In one study, the range was between 15 days with a baseline viral load of 1,000 compared to 113 days with a baseline of 1 million viral copies/ml (Rizzard et al. 2000). The following figure shows the typical biphasic decrease in viral load after initial high levels (in this case almost 4 million copies/ml).

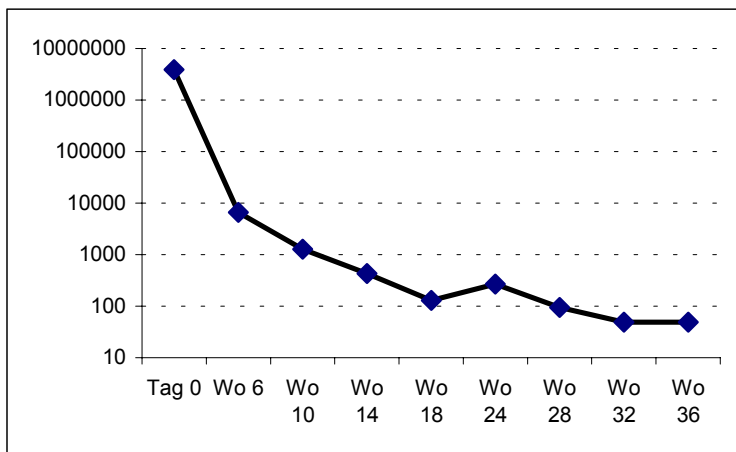


Figure 1: Typical biphasic decrease in viral load on HAART. Viral load was initially very high, and reached a level below 50 copies/ml only at week 32. Note the temporary increase at week 24, which is possibly due to methodological variability. HAART was not changed.

Numerous studies have focused on whether durable treatment success can be predicted early in treatment (Demeter et al. 2001, Kitchen et al. 2001, Lepri et al. 2001, Thiabut et al. 2000). In a study of 124 patients, a decrease of less than 0.72 log after one week was predictive of virological treatment failure in more than 99 % of patients (Polis et al. 2001). However, this has little clinical relevance, and in our opinion, to start

measurement of viral load only one or two weeks after initiation of therapy is pointless.

In the first few months, we measure viral load every four weeks until it has dropped below the level of detection – the most important goal! After this, viral load can be measured every three months. In case of rebound, closer monitoring becomes necessary.

Following initiation of therapy, viral load should be below 5,000 copies/ml after one month. Higher values are predictive of failure to reach levels below detection (Maggiolo et al. 2000).

Practical tips for dealing with viral load

- Use only one assay, if possible.
- Use only one experienced laboratory, if possible.
- Watch for assay variability (up to half a log) and explain this to the patient!
- Monitor viral load every four weeks with new HAART, until the viral load is below the level of detection (50 copies/ml).
- Then measure viral load at greater intervals – on successful HAART every three months is sufficient.
- Without HAART, measurement every three months is sufficient.
- Don't measure shortly after vaccinations or with concurrent infections.
- Implausible results should be rechecked after 2-4 weeks. Remember differences between subtypes (in some cases it may be useful to use another method).

(see also "Goals and Principles of Therapy")

Viral load can also be measured fairly reliably in body fluids other than blood or plasma (for example cerebrospinal, vaginal or seminal fluid). However, such tests are usually performed for scientific purposes and are not routine.

CD4+ Cells

CD4+ cells are T-lymphocytes expressing the CD4 receptor on their surface. This lymphocyte subpopulation is also referred to as T helper cells. Alongside viral load, measurement of the CD4+ cell level is the most important parameter or surrogate marker in HIV medicine. It allows for a reliable estimation of the individual risk for AIDS. Every HIV patient should have had a CD4+ cell measurement within the last six months! Two reference values are generally accepted: above 400-500 CD4+ cells/ μ l, severe AIDS-related diseases are very rare; below 200 CD4+ cells/ μ l, the risk for AIDS-related morbidity increases significantly with increased duration of immunosuppression.

Several points should be considered when measuring CD4+ cells (usually by flow cytometry). Blood samples should be processed within 18 hours. The lower normal values are between 400 and 500 cells/ μ l, depending on the laboratory. Samples should always be sent to only one (experienced) laboratory. The higher the level of CD4+ cells, the greater the variability. Differences of 50-100 cells/ μ l are not unusual. In one study, the 95 % confidence intervals with a real value of 500/ μ l were between 297 and 841/ μ l. At 200 CD4+ cells/ μ l, the 95 % confidence interval was between 118 and 337/ μ l (Hoover 1993).

Measurement of CD4+ cells should only be repeated in the case of highly implausible values. As long as the viral load remains below the level of detection, there is no need to be concerned, even with greater decreases in CD4+ cells. In such cases, the relative values (CD4+ percentages) and the CD4+/CD8+ ratio (ratio of CD4+ cells to CD8+ cells) should be referred to; these are usually more robust and less prone to fluctuation. As a general point of reference: with values > 500 CD4+ cells/ μ l, > 29

% is to be expected, with < 200 CD4+ cells/ μ l $< 14\%$. The normal ranges for the relative values and the ratio may be defined differently by individual laboratories.

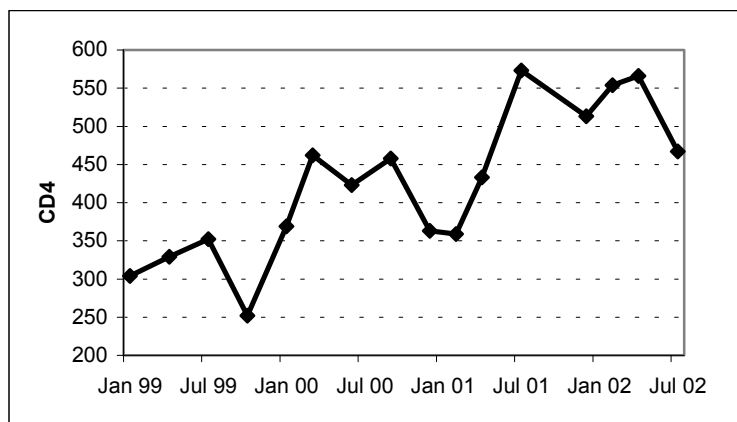


Figure 2. Patient example for variations in absolute CD4+ cells/ μ l over a period of four years. The viral load was continuously below 50 copies/ml, HAART remained unchanged.

Clinicians sometimes forget that for the patient the result of the CD4+ cell count is often of existential importance. To go to the doctor and discuss the test results involves a great deal of stress for many patients (“worse than getting grades”). Unreflectedly informing the patient of a bad result can lead to reactive depression. From the start, patients must be informed about the possible physiological and method-related variability of laboratory tests. In the case of unexpectedly good results, every effort should be made to contain premature euphoria. In the long run this saves time and discussions, and the patient is spared unnecessary ups and downs. We do not consider it advisable for non-physician personnel (without extensive HIV experience) to inform patients of results.

Once CD4+ cell counts within the normal range are reached, in our opinion half-yearly measurements suffice.

Influencing factors

Several other factors influence CD4+ cell counts apart from laboratory-related variabilities. These include concurrent infections, leukopenia of varying etiology, and steroids or other immunosuppressive therapies. Extreme exertion (marathons!), surgical procedures or pregnancy can also lead to lower values. Even diurnal variation occurs; CD4+ cells are lower at noon, and highest in the evening around 8 p.m. (Malone et al. 1990). Psychological stress seems to play a negligible role, even though patients often assume the contrary.

Kinetics of CD4+ cells on HAART

Similarly to viral load, a biphasic increase in CD4+ cells occurs following the initiation of HAART (Renaud et al. 1999, Le Moing et al. 2002), with a rapid increase within the first three to four months and a much slower rise thereafter. In a study of almost 1,000 patients, the CD4+ cell count increased by 21/ μ l per month during the first three months. In the following 21 months, this rate was only 5.5 CD4+ cells/ μ l per month (Le Moing et al. 2002). The initial rapid increase in CD4+ cells is probably due to redistribution, which is followed by the new production of naive T cells (Pakker et al. 1998). Diminished apoptosis may also play a role (Roger et al. 2002).

Several factors can influence the extent of immune reconstitution during HAART. The degree of viral suppression is crucial – the lower the viral load, the more pronounced the effect (Le Moing et al. 2002). The absolute increase is higher if initial CD4+ cell counts were high (Kaufmann et al. 2000). Naive T cells still present at initiation of therapy are a particularly important factor for long-term immune reconstitution (Notermans et al. 1999).

Age is also important. The larger the thymus and the more active the process of thymopoiesis, the more significant the rise in

CD4+ cells is likely to be (Kolte et al. 2002); due to age-related degeneration of the thymus, CD4+ cells in older patients do not increase as much as those in younger ones (Viard et al. 2001). However, we have seen both 20 year-old patients with completely insufficient CD4+ count recover and 60 year-old patients with very good increases in CD4+ cells.

Beyond measurement of CD4+ cell count, a number of other assays allow detailed testing of the qualitative or functional capacity of the immune system, for example in response to specific antigens (Gorochov et al. 1998, Lederman 2001, Lange et al. 2002). A good review was recently published (Telenti 2002). These methods are not currently necessary for routine diagnostics.

Practical tips for dealing with CD4+ cells

- As with viral load: use only one (experienced) laboratory.
- The higher the values, the greater the variability (consider numerous influential factors) – compare the relative (percentage) values and CD4+/CD8+ ratio with previous results!
- Do not disconcert the patient with apparent decreases – if viral suppression is sufficient, the drop is usually not HIV-related! Only highly implausible results should be repeated.
- If the viral load is below the level of detection, three-monthly measurements of CD4+ cells are sufficient.
- CD4+ count and viral load should always be discussed by the physician.

Other Routine Checks – What Should Be Monitored during the Year?

Beside CD4+ count and viral load, several other parameters should be monitored in the HIV patient. The following recommendations apply for clinically asymptomatic patients with

normal results in routine laboratory evaluations, who have been on stable treatment for several months or are not taking antiretroviral therapy. Of course, if treatment is started or changed, or if the patient develops complaints, more frequent monitoring is required. Depending on the problem, additional tests may be necessary. A complete physical examination should be performed regularly, and this often leads to the discovery of a Kaposi lesion or a mycosis (thrush!). The lower the CD4+ cells, the more frequently patients should be examined.

Table 10.2: Minimal evaluations per year in stable asymptomatic patients

	Patient on ART Per year	Untreated Per year
Blood count, LDH, ALT, AST, creatinine, bilirubin, alk. phosphatase, lipase, γ GT, glucose	4-6 x	2-4 x
Viral load	4 x	2-4 x
CD4+ cells	2-4 x	2-4 x
Lipids	1-2 x	1 x
Physical examination	2-4 x	1-2 x
Gynecological examination	1 x	1 x
Fundoscopy if CD4+ cells < 200/ μ l	2-4 x	4 x (and HAART!)

In patients with < 200 CD4+ cells/ μ l, we usually perform fundoscopies every three to six months to exclude CMV retinitis. Close cooperation with an experienced ophthalmologist is important. The better the CD4+ cells, the less often fundoscopies are necessary. Regular gynecological examinations with PAP smears are also recommended (see also the European guidelines: <http://hiv.net/link.php?id=185>). However, such guidelines are interpreted very differently.

In our experience, unless there is a specific suspicion, routine X-rays, ultrasound examinations, multiple serologies or measurements of lactate are not necessary. Especially in cases of

good immune status, patients can sometimes just be left in peace!

An annual ECG is only indicated in our view in patients with a specific risk profile (see also the chapter “HIV and cardiac disease”). The tuberculin test (the Mendel-Mantoux skin test with 5 IE once a year) should only be repeated if it is negative initially.

Therapeutic Drug Monitoring (TDM) – When Should Plasma Levels Be Measured?

Individual plasma levels of many antiretroviral drugs may vary quite considerably for differing reasons (e.g. compliance, metabolism, absorption). But, sufficient plasma levels are essential for virological treatment success (Acosta et al. 2000). In the VIRADAPT Study, adequate PI-concentrations were even more crucial than knowledge of resistance mutations (Durant et al. 2000). The importance of sufficient plasma levels has also been shown for NNRTIs (Marzolini et al. 2001, Veldkamp et al. 2001).

On the other hand, very high plasma levels correlate with a higher rate of side effects. Reported renal problems with indinavir (Dieleman et al. 1999), gastrointestinal disturbances with ritonavir (Gatti et al. 1999), hepatotoxicity with nevirapine (Gonzalez et al. 2002), or CNS problems with efavirenz (Marzolini et al. 2001) were all associated with high plasma levels. We have observed that patients developing a rash on nevirapine also had high plasma concentrations.

The measurement of drug concentrations in serum or plasma (therapeutic drug monitoring, TDM) has therefore become an important tool for monitoring therapy. The best reviews are to be found in Back et al. 2002 and Burger et al. 2002. Due to the increasing complexities of antiretroviral combinations, TDM of protease inhibitors and NNRTIs will probably become more important in the future.

Several problems associated with TDM are limiting its broader use. The measurement of nucleoside analogs, for example, is senseless since they are converted to the active metabolites only intracellularly. Measuring NNRTIs or PIs may therefore determine levels of only one component of a (failing) combination. Further problems include not only viral strains with different levels of resistance, different inhibitory concentrations, variable protein binding, and time-dependent variability of plasma levels, but also methodological problems with the assays, as well as the lack of clearly defined limits. Many uncertainties thus remain in the assessment of therapeutic drug levels. Until data from randomized studies is available proving the clinical value of TDM, both measurement and interpretation of the results should be left to specialized centers.

Measurement of plasma levels is currently recommended in the following situations:

- Complex drug combinations and concomitant medications that could lead to interactions
- Lack of efficacy of a drug or a combination
- Suspected absorption problems
- Occurrence of toxic effects
- Significantly impaired liver function

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Chapter 4:

Management of Side Effects

Christiane Schieferstein

Side effects on HAART are a common problem in HIV medicine. As a result, treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicities. More than half the patients switch therapies within the first few months on HAART because of side effects. Roughly 20 % of all patients refuse to even begin HAART due to concerns regarding the side effects (Higleyman 2000).

The patient should be counseled in detail on the potential side effects, so that he or she is in a position to recognize them and – in certain cases – to consult the treating clinician in time. This can save lives, for example in the case of the abacavir hypersensitivity reaction, and the irreversible damage of side effects, such as polyneuropathy, can be prevented through early diagnosis. Being prepared for the occurrence of possible problems and providing potential solutions improves both the acceptance of treatment and compliance. However, patients should not be frightened by all this information – the extensive package inserts are often ominous enough. It may be difficult to distinguish between symptoms related to HIV infection and those caused by antiretroviral therapy. An accurate history, including any co-medication (including over-the-counter products!) is paramount. The intensity, variation and reproducibility of complaints are important to consider – before symptoms are judged as being side effects of treatment, other possible causes should be excluded.

It must be stressed that the majority of patients are able to tolerate HAART well, even over years. Nevertheless, the monitoring of treatment by an HIV clinician, even in asymptomatic patients, is recommended in at least three-monthly intervals. Stan-

Standard evaluations include taking the history, the physical examination and measurement of vital signs and body weight.

Gastrointestinal Side Effects

Gastrointestinal side effects are the most common side effects of almost all antiretroviral drugs – nucleoside analogs, NNRTIs and particularly protease inhibitors – and occur especially during the early stages of therapy. Typical symptoms include abdominal discomfort, loss of appetite, diarrhea, nausea and vomiting. Heartburn, abdominal pain, meteorism and constipation may also occur. Nausea is a common symptom with zidovudine-containing regimens; diarrhea occurs frequently with zidovudine, didanosine and all PIs, particularly nelfinavir, as well as with saquinavir and lopinavir/r.

In addition to the often considerable impact on everyday life, gastrointestinal side effects can lead to dehydration, malnutrition with weight loss and low plasma drug levels.

In most cases, symptoms occur at the start of therapy. Patients should be informed that these side effects usually resolve after four to six weeks of treatment. If gastrointestinal side effects occur for the first time after longer periods on HAART, other causes are likely.

If administration on an empty stomach leads to **nausea and vomiting**, most drugs can also be taken together with meals. When a drug (e.g. didanosine, indinavir, rifampin) has to be administered on an empty stomach, small quantities of low-fat salty crackers may lessen the nausea. Ginger, peppermint or chamomile teas or sweets may also be helpful. Care should be taken with fatty foods and dairy products. Coffee, smoking, alcohol, aspirin and very spicy foods should be avoided if possible.

If symptomatic treatment is necessary, metoclopramide has been proven to be useful. Dimenhydrinate, cimetidine, ranitidine or ondansetron can also be used. Antiemetic drugs should not be administered as required, but taken regularly, ideally 30–

45 minutes before HAART. After a few weeks, doses can generally be slowly reduced.

In the case of **diarrhea**, other causes such as infections or lactose intolerance should be excluded. Oat bran tablets have been proven to be useful and cheap for PI-associated diarrhea. They are taken together with antiretroviral therapy (daily dose 1500 mg). Alternatively, psyllium may be effective. Nelfinavir-associated diarrhea is alleviated by calcium, taken as calcium carbonate, at a dosage of 500 mg bid.

The cornerstone of symptomatic treatment is loperamide which inhibits bowel movement (initially 4 mg, followed by 2 mg, up to a maximum of 16 mg daily). If loperamide is not effective, opium tincture is an alternative. Pancrelipase, a synthetic pancreatic enzyme, has also been shown to be effective for PI-associated diarrhea. In some cases, a combination of different drugs may be appropriate.

If significant dehydration and loss of electrolytes occur, coke and salty crackers, sport drinks, herbal teas or electrolyte solutions may be taken (reviews in: Sherman et al. 2000, Bartlett et al. 2001, Carr et al. 2001, Highleyman 2002, Schwarze 2002).

CNS Disorders

In up to 40 % of patients, treatment with efavirenz leads to CNS side effects such as dizziness, insomnia and nightmares; even mood changes, depression and depersonalization may occur. These side effects are observed mainly during the first days and weeks of treatment. Discontinuation of therapy becomes necessary in only 3 % of patients. There is an association between high plasma levels of efavirenz and the occurrence of CNS symptoms (Marzolini et al. 2001). Lorazepam can diminish these side effects, and haloperidol can be given for panic attacks and nightmares. Patients should be informed about the nature of these symptoms, and that they are usually expected to resolve after a short period of time. These side effects are rarely seen with other NNRTIs (Highleyman 2000).

Peripheral Polyneuropathy

Peripheral polyneuropathy is caused mostly by the nucleoside analogs zalcitabine, didanosine and stavudine. It usually presents with a distal symmetrical distribution and sensorimotor paralysis. Patients complain of paresthesia and pain in their hands and feet, which often begin gradually after several months of therapy. HIV infection itself can lead to peripheral polyneuropathy, but the drug-induced form becomes apparent much earlier and may develop within a shorter period of time. Patients should be informed that they should consult their treating physician as soon as possible if the typical complaints develop.

Additional risk factors for polyneuropathy, such as vitamin B12 deficiency, alcohol abuse, diabetes mellitus or treatment with other neurotoxic drugs, e.g. INH, should be addressed in the appropriate manner.

Symptoms frequently improve within the first two months following discontinuation of the responsible drugs, but may initially increase in intensity and are not always fully reversible. Treatment is difficult, and there is no specific therapy.

Apart from symptomatic treatment, methods such as acupuncture or transcutaneous nerve stimulation have been tried with variable success. Tight shoes or long periods of standing or walking should be avoided; cold showers may relieve pain before going to bed. The role of recombinant human nerve growth factors is still to be defined (McArthur et al. 2000).

Renal Problems

Renal problems occur particularly on indinavir treatment, and are caused by indinavir crystals, which may be found in the urine of up to 20 % of patients. Approximately 10 % of patients develop a nephrolithiasis, which is not visible on X-ray, accompanied by renal colics. Renal failure is rare (Olyaei et al. 2000, Kopp 2002). Symptoms of acute colic include back pain and

flank pain as well as lower abdominal pain, which may radiate to the groin or testes. Hematuria may also occur. Evaluations should include a physical examination, urine and renal function tests and an ultrasound. For acute therapy, i.v. analgesia (e.g. metamizole 1 to 2.5 g) or diclofenac (e.g. 100-150 mg) may be given in combination with spasmolytic drugs (e.g. butylscopolamine, 20 mg i.v.). This usually relieves the symptoms quite rapidly, and may be repeated after a few minutes if symptoms persist. If this is unsuccessful, pethidine 50-100 mg i.v. or i.m. can be administered. Fluids should be given in moderation during colics.

For prophylaxis, a daily intake of 1.5 l of fluids is recommended, which should be increased during hot weather and on consumption of alcohol. Interruption of therapy following a single incidence of colic is not usually necessary. With recurring colics, however, indinavir should be discontinued.

Nonsteroidal anti-inflammatory drugs, quinolones, ampicillin, foscarnet, aciclovir, sulfonamides (cotrimoxazole, sulfadiazine) and allopurinol can also cause nephrolithiasis, and should therefore be used with caution in combination with indinavir (Bou-baker et al. 1998).

Hepatotoxicity

Elevated liver function tests may be caused by drugs, viral hepatitis or alcohol abuse. They occur in 2-18 % of patients on HAART, independent of the drug classes used (Bartlett et al. 2001). Severe hepatotoxicity and hepatic failure have been observed during treatment with nevirapine, and the PIs, indinavir and ritonavir – patients with pre-existing liver disease should receive these drugs only under strict monitoring (Sulkowski et al. 2000/2002).

Hepatotoxic reactions occur at different time points for different drug classes: nucleoside analogs lead to hepatic steatosis, which is probably caused by mitochondrial toxicity and usually occurs after more than 6 months on treatment (Carr et al. 2001).

NNRTIs often cause a hypersensitivity reaction within the first 12 weeks. In one study, severe hepatotoxicity was observed in 15.6 % of patients on nevirapine and 8 % of patients on efavirenz. Those patients who were concurrently taking PIs and were coinfecting with hepatitis B virus and/or hepatitis C virus had the highest risk (Sulkowski et al. 2002). PIs can lead to hepatotoxicity at any stage during the course of treatment – once again, patients with chronic viral hepatitis are particularly at risk. One possible cause is an immune reconstitution syndrome on HAART, with increased cytolytic activity against the hepatitis viruses. Among the PIs, toxic hepatitis is seen most frequently in patients on ritonavir (Sulkowski et al. 2000).

Liver functions tests should be monitored biweekly at the start of treatment with nevirapine and PIs (more frequently in patients with pre-existing liver disease). Monthly tests are generally sufficient for all other drugs. If liver enzymes (ALT, AST) are moderately elevated (< 3.5 times the upper limit of normal) in the absence of clinical symptoms, treatment can be continued under close monitoring. If liver enzymes are elevated to more than 3.5 times the upper limit of normal, additional diagnostic tests should be performed, including an abdominal ultrasound. In cases of co-infection with hepatitis B or C, treatment of these conditions should be considered. With other pre-existing liver conditions, it may be useful to determine drug plasma levels. Discontinuation of treatment may not be necessary.

Anemia, Leukopenia

5 to 10 % of patients taking zidovudine develop anemia (Carr et al. 2001). Neutropenia occurs less frequently. Most commonly affected are patients with advanced HIV infection and pre-existing myelosuppression, on chemotherapy or co-medication with other myelotoxic drugs. Monthly monitoring of blood count is important, as anemia may develop even after years on treatment. In cases of severe anemia, zidovudine should be discontinued; rarely, a blood transfusion may be necessary. Treat-

ment with erythropoietin or G-CSF is an option, but should be avoided as a long-term option if possible, due to the associated high costs. Anemia is observed less frequently with stavudine, lamivudine and abacavir; leukopenia may occur on indinavir, abacavir or tenofovir. For more information on thrombocytopenia, see the chapter entitled “HIV-associated thrombocytopenia”.

Allergies

Allergies occur approximately 100 times more frequently in HIV infected individuals than in the general population (Roujeau et al. 1994). Allergies against antiretroviral drugs occur with all the NNRTIs, as well as with the nucleoside analog, abacavir (see below) and the PI, amprenavir. Nevirapine and delavirdine may cause a slight rash in 15 to 20 % of patients, 7 % of which discontinue treatment. The rash is seen less frequently with efavirenz, with which only 2 % of the patients discontinue the drug (Carr et al. 2001). Abacavir causes a hypersensitivity reaction in approximately 2-4 % of patients, which may be life-threatening (review in Hewitt 2002). A genetic predisposition for the hypersensitivity reaction (HSR) to abacavir has been discussed. Two studies have found a correlation between the HLA-type (particularly HLA-B 57) and the occurrence of the HSR (Hetherington et al. 2002, Mallal et al. 2002).

Allergies to NNRTIs

The NNRTI allergy is a reversible, systemic reaction and typically presents as an erythematous, maculopapular, pruritic and confluent rash, distributed mainly over the trunk and arms. Fever may precede the rash. Further symptoms include (partly severe) myalgia, fatigue and mucosal ulceration. The allergy usually begins in the second or third week of treatment. If symptoms occur after 8 weeks of initiation of therapy, other drugs should be suspected. Severe reactions such as the Stev-

ens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) or anicteric hepatitis are rare.

Approximately 50 % of NNRTI allergies resolve despite continuation of therapy. Antihistamines may be helpful. Treatment should be discontinued immediately in cases with mucous membrane involvement, blisters, exfoliation, hepatic dysfunction (transaminases > 5 times the upper limit of normal) or fever > 39°C.

Prophylactic treatment with glucocorticosteroids showed no benefit for prevention of nevirapine allergy in a double-blind, placebo-controlled study (Knobel et al. 2001).

Abacavir Hypersensitivity

The rash associated with the abacavir hypersensitivity reaction (HSR) is often discrete, in contrast to the skin reactions to nevirapine and efavirenz; in 30 % of patients it may not occur at all (Hewitt 2002). 80 % of patients have fever. In addition to a general malaise (which gets worse from day to day!), other frequent symptoms include gastrointestinal side effects such as nausea, vomiting, diarrhea and abdominal pain. Respiratory symptoms such as dyspnea, cough and sore throat are rare. Changes in the blood count, elevation of liver transaminases, alkaline phosphatase, creatinine and LDH may accompany the HSR. There is usually no eosinophilia. One case of Stevens-Johnson syndrome has been described (Bossi et al. 2002). The HSR occurs after a median of 8 days, and within the first 6 weeks in 93 % of cases.

The HSR is diagnosed clinically. The differential diagnosis from an intercurrent infection is often difficult. Criteria in favor of HSR include the development of symptoms within the first 6 weeks of treatment, deterioration with each dose taken and the presence of gastrointestinal side effects.

If abacavir is discontinued in time, the HSR is completely reversible within a few days. If the HSR is not diagnosed, it may

be fatal. After discontinuation of abacavir, further supportive treatment includes intravenous hydration and possibly steroids.

Once the diagnosis of HSR has been established, rechallenge with abacavir can be fatal and is strictly contraindicated. If there was only a vague suspicion of HSR, in-patient rechallenge is possible. When treatment has been interrupted, it should be noted that the HSR can occur after restarting treatment, even without a prior HSR.

Treatment with abacavir requires detailed counseling on the possible occurrence and symptoms of the HSR. Patients should know who to contact in cases of suspected HSR, preferably also at night and on weekends. It is important, however, not to frighten patients to the extent that they themselves discontinue treatment too early.

Lactic Acidosis

In comparison to asymptomatic hyperlactacidemia, which occurs in approximately 15 % of NRTI-treated patients (Carr et al. 2001, Gerard et al. 2000), lactic acidosis is a rare but life-threatening complication. It occurs most frequently on treatment with stavudine and didanosine. Risk factors are obesity, female sex and pregnancy. NRTIs are thought to cause mitochondrial toxicity via inhibition of the mitochondrial DNA polymerase. The incidence is approximately 3.9/1000 NRTI patient years (John et al. 2001).

The clinical symptoms, such as fatigue, nausea and vomiting, abdominal pain, weight loss and dyspnea are very unspecific and may develop acutely or more gradually. Blood results show elevated lactate levels with or without metabolic acidosis (blood should be taken in a cooled fluoride oxalate tube, with transport on ice and measurement of lactate within 4 hours). CPK, LDH, lipase, amylase, γ GT and the anion gap may be increased; serum bicarbonate may be decreased. Hepatic steatosis can often be seen on ultrasound or CT.

One study showed that serum lactate levels rise significantly after initiation of NRTI therapy, and then remain stable, between 1.5 and 3 mmol/l (John et al. 2001). Cases of severe lactic acidoses occurred without prior symptomatic hyperlactacidemia. Lactate levels should therefore not be monitored routinely, as increases are not predictive and may lead to unnecessary changes in treatment (Brinkman 2000). In contrast, lactate levels should be tested immediately in symptomatic patients complaining of fatigue, sudden weight loss, abdominal disturbances, nausea, vomiting or sudden dyspnea.

For lactate levels between 2 and 5 mmol/l, "watchful waiting" with regular monitoring is recommended (see Brinkman 2001). If the resistance profile allows, NRTI treatment may be modified, e.g. switch from d4T/ddI to abacavir, zidovudine or tenofovir. At levels above 5 mmol/l, NRTI treatment should be stopped immediately and supportive treatment initiated; for example, correction of the acidosis. The mortality of patients with lactate levels above 10 mmol/l is approximately 80 % (Carr et al. 2001).

Different drugs have been used to treat lactic acidosis with limited success, including vitamin B-complex, coenzyme Q10, vitamin C and L-carnitine. These treatment approaches are based on case reports, not studies. In one small study, 6 patients were successfully treated with intravenous vitamin B-complex (100 mg thiamine, 20 mg riboflavin, 200 mg nicotinamide, 20 mg pyridoxine, 20 mg dexapanthanol) plus L-carnitine (1000 mg) twice daily (Brinkman 2000). This treatment is given intravenously until lactate levels fall below 3 mmol/l, and is then continued orally. Normalization of lactate takes an average of 8 weeks after therapy has been discontinued (Bartlett et al. 2001).

Pancreatitis

In addition to lactic acidosis, pancreatitis is a further potentially fatal complication, probably caused by mitochondrial toxicity. It is not distinguishable from pancreatitis of any other etiology,

either clinically or in laboratory tests. It is caused mainly by didanosine, and occasionally by stavudine, lamivudine and zalcitabine. The combination of stavudine plus didanosine plus hydroxyurea carries a particularly high risk for pancreatitis. Alcohol consumption and treatment with pentamidine are further risk factors.

Antiretroviral therapy should be stopped immediately. Treatment is the same as for pancreatitis of other etiologies. The symptoms and laboratory changes usually resolve rapidly (Carr et al. 2001).

Avascular Necrosis

Avascular necrosis occurs in approximately 0.4 % of HIV patients, and is therefore significantly more frequent than in the general population (Cheonis 2002). An association with PIs has been postulated, so far without proof of a direct correlation. Risk factors for avascular necrosis are alcohol abuse, hyperlipidemia, steroid treatment, hypercoagulability, hemoglobinopathy, trauma, nicotine abuse and chronic pancreatitis.

The most common site of the necrosis is the femoral head and, less frequently, the head of the humerus. Initially, patients complain of pain when weight-bearing on the affected joint, with symptoms worsening over days and weeks. The initial stages may be asymptomatic, but are followed by severe bone pain and reduced mobility. Necrosis of the femoral head produces pain in the hip or groin, which may radiate to the knee.

All patients on HAART, especially those with additional risk factors (steroids!) should be monitored closely if hip pain occurs for the first time. Even in subjects with moderate bone or joint pain, an MRI should be performed early on. MRI is more sensitive than conventional radiography. Early diagnosis and treatment can spare patients pain, loss of mobility and surgical interventions.

If the diagnosis is confirmed, patients should be referred to an orthopedic surgeon as soon as possible. There are different

treatment strategies available, which reduce bone and joint damage as well as pain, and which depend on the stage of disease, localization and grade of severity. In the early stages, reduced weight bearing with crutches is often sufficient. Surgical core decompression is an option: several holes are drilled in the femoral neck or head, causing new blood vessels to develop and thereby reducing the pressure within the bone. In the more advanced stages, the chances of success decrease with the size of the necrosis. The alternative – osteotomy – has the disadvantage of reducing the mobility of patients over long periods of time. In severe cases, a total endoprosthesis (TEP) is usually necessary.

Further risk factors need to be identified and eliminated. If possible, steroids should be discontinued and the treatment with PIs modified. Physiotherapy is recommended. Nonsteroidal anti-inflammatory drugs (e.g. ibuprofen) are the treatment of choice for analgesia.

Osteopenia/Osteoporosis

HIV infected individuals have a lower bone density than uninfected individuals. Bone density is determined by the measurement of X-ray absorption (e.g. DEXA scan) or ultrasound waves. Results are given as the number of standard deviations (the T-score) from the mean value in young, healthy individuals. Values between -1 and -2.5 standard deviations (SD) are referred to as osteopenia, values above -2.5 SD as osteoporosis.

In addition to HIV infection, other factors such as malnutrition, diminished fat tissues, steroid treatment, immobilization and treatment with PIs and NRTIs seem to play a role in the pathogenesis of this disorder. Osteopenia and osteoporosis are often asymptomatic. Osteoporosis occurs mainly in the vertebrae, lower arms and hips.

The following tests should be performed on all patients with AIDS: a lumbar spine X-ray in the standard anteroposterior and lateral views; bone density measurement (DEXA scan) of the

lumbar spine and hip; and laboratory blood tests, including calcium, phosphate and alkaline phosphatase. Osteopenia should be treated with 1000 I.E. vitamin D daily and a calcium-rich diet or calcium tablets with a dose of 1200 mg/day. Patients should be advised to exercise and give up alcohol and nicotine. In cases with osteoporosis, aminobiphosphonates may be added (Bartl 2002, Tebas et al. 2000, Cheonis 2001).

Lipodystrophy, Dyslipidemia

The long-term side effects of HAART include metabolic disorders such as lipodystrophy, hyperlipidemia and insulin resistance. There are multiple disorders for which the etiology is not clearly established. Many disorders cannot be attributed to individual drugs or classes of drug. For details see the chapter entitled “Lipodystrophy syndrome”.

Hyperglycemia, Diabetes mellitus

Whereas hyperlipidemia is usually observed within the first months of therapy, elevated blood glucose levels may also be seen later. Hyperglycemia is caused by insulin resistance, as in type II diabetes. The mechanism is probably a treatment-related impairment of glucose transport and/or influence on intracellular phosphorylation of glucose. Hyperglycemia occurs on PI-treatment – especially with indinavir – and, less frequently, on NRTIs (Hardy et al. 2001, Modest et al. 2001). Older age, a higher body-mass-index, hypercholesterinemia and hypertriglyceridemia are associated with an increased risk of developing insulin resistance. Patients with these risk factors or pre-existing diabetes mellitus require close monitoring. Patients should be informed about the warning symptoms of polydipsia, polyphagia and polyuria.

Blood glucose levels decrease once therapy has been discontinued. Whether or not they will eventually return to normal is, as yet, unclear. There is insufficient data so far to determine whether or not PI-treatment should be discontinued in newly

diagnosed diabetes mellitus. Overt diabetes mellitus with ocular, renal and cardiovascular complications is rare.

Increased Bleeding Episodes in Hemophiliacs

HIV patients with hemophilia A or B, on treatment with protease inhibitors, may have increased episodes of spontaneous bleeding into joints and soft tissues. Rarely, intracranial and gastrointestinal bleeding has occurred, a median of 22 days after starting therapy. The etiology is unclear (Bartlett et al. 2001).

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Chapter 5:

The Lipodystrophy Syndrome

Georg M. N. Behrens and Reinhold E. Schmidt

Background

The HIV lipodystrophy syndrome is of major importance in HIV-therapy, not least because of its high prevalence. There is now good evidence that the metabolic abnormalities harbor a significant risk for cardiovascular disease with as yet unknown consequences. In addition, several studies report a reduced quality of life in patients with body habitus changes leading to reduced therapy adherence. Despite the impact of the lipodystrophy syndrome on HIV management, little is known about the pathogenesis, its prevention, diagnosis and treatment. Current data indicate a rather multifactorial pathogenesis where HIV infection, its therapy, and patient-related factors are major contributors. The lack of a clear definition reflects the clinical heterogeneity, limits a clear diagnosis and impairs the comparison of results among clinical studies. Therapeutic and prevention strategies have so far been of only limited or no success. Thus, general recommendations include dietary changes and physical activity, altering antiretroviral drug therapy (replacement of protease inhibitors with NNRTI or switch from d4T to AZT or abacavir), and finally, the use of metabolically active drugs. Here we summarize the pathogenesis, diagnosis and treatment options of the HIV-lipodystrophy syndrome based on the current literature.

Clinical Manifestation

Lipodystrophy was originally described as a condition characterized by regional or generalized loss of subcutaneous fat. The non-HIV-associated forms, like congenital or familial partial

lipodystrophy, are of very low prevalence. Generally, these forms are associated with complex metabolic abnormalities and are difficult to treat. The term "lipodystrophy syndrome" in HIV was introduced for a complex medical condition including the apparent abnormal fat redistribution and metabolic disturbances seen in HIV-patients receiving protease inhibitor therapy (Carr et al. 1998). Since then, other conditions, such as osteopenia and hyperlactemia, have been summarized under the diagnosis of the lipodystrophy syndrome. But, even years after its first description, there is still no consensus on a case definition for lipodystrophy syndrome in HIV patients. Thus, the diagnosis of lipodystrophy often relies on a more individual interpretation than on an evaluated classification. Finally, changes in the fat distribution have to be considered as being rather dynamic processes with variable features and an inconsistent intensity over time.

HIV-associated lipodystrophy includes both clinical and metabolic alterations. The most prominent clinical sign is a loss of subcutaneous fat (lipoatrophy) in the face (periorbital, temporal), and the extremities. The latter occasionally leads to prominent veins resembling varicosis. Peripheral fat loss can be accompanied by an accumulation of visceral fat which can cause mild gastrointestinal symptoms. Visceral obesity, as a singular feature of abnormal fat redistribution, appears to occur in only a minority of patients. In contrast to earlier descriptions, dorso-cervical fat pads in HIV patients seem to be larger in comparison to those found in control populations but do not have a higher prevalence (Zolopa et al. 2003). Female HIV-patients sometimes complain about painful breast enlargements which have been attributed to the lipodystrophy syndrome. Whether gynecomastia in male patients is a component of the syndrome remains unclear. There is now accumulating evidence that the major clinical components - lipoatrophy, central adiposity and the combination of both - result from different pathogenetic developmental processes.

The prevalence of the lipodystrophy syndrome has been estimated to be between 30 and 50% based on cross-sectional studies. A prospective study over an 18 month period revealed a prevalence of 17%. Lipodystrophy has been observed most frequently in patients receiving a protease inhibitor containing regimen although almost all antiretroviral drug combinations can be associated with fat redistribution. The risk of the syndrome increases with the duration of treatment, the age of the patient and the level of immunodeficiency. Lipodystrophy has been observed during the therapy of both the acute and chronic states of HIV infection and even following post-exposure prophylaxis. Children can be affected, like adults, with clinical fat redistribution shortly after initiation or change of antiretroviral therapy. The evolution of the individual clinical components of the lipodystrophy syndrome is variable. Subcutaneous fat loss has been observed during exclusive therapy with NRTIs but develops faster under a combination of NRTIs and protease inhibitors. Single case reports even describe body habitus changes compatible with the lipodystrophy phenotype in antiretroviral therapy-naïve patients.

Frequently, complex metabolic alterations are associated with the described body shape alterations. These include peripheral and hepatic insulin resistance, impaired glucose tolerance, diabetes type 2, hypertriglyceridemia, hypercholesterolemia, increased free fatty acids (FFA), and decreased high density lipoprotein (HDL). Often these metabolic abnormalities appear or deteriorate before the manifestation of fat redistribution. The prevalence of insulin resistance and glucose intolerance has been reported in the literature at 20 to 50% depending on the study design and measurement methods. Lipodystrophic patients present with the highest rates of metabolic disturbances. Frank diabetes is less frequent with a prevalence of between 1 and 6%.

Hyperlipidemias are a frequently observed side effect of antiretroviral therapy, especially in combinations including protease inhibitors. Given that many HIV patients present with already

decreased HDL levels, these are not further reduced by antiretroviral drugs. Hypertriglyceridemias are the leading lipid abnormality either alone or in combination with hypercholesterolemia. Lipid levels usually reach a plateau and remain stable after several weeks following the initiation or change of the HIV-therapy. All protease inhibitors potentially lead to hyperlipidemia, although to different extents. For example, Agenerase (Amprenavir[®]) appears to be less frequently associated with dyslipidemia. In contrast, ritonavir (Norvir[®]) often leads to hypertriglyceridemia correlating to the drug levels. Increases of 200% in triglyceride levels and of 30-40% in cholesterol levels have been described following short-term ritonavir therapy. Similar observations were made in healthy individuals.

The therapy-induced dyslipidemias are characterized by increased low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL). Detailed characterization revealed an increase of apolipoprotein B, CIII and E. Raised levels of lipoprotein (a) have been described in protease inhibitor recipients. Mild hypercholesterolemia can occur during therapy with efavirenz (Sustiva[®], Stocrin[®]) but is not typical under therapy with nevirapine (Viramune[®]) or NRTIs. It is important to note that HIV infection itself is associated with disturbed lipid metabolism. During disease progression, the total cholesterol and HDL levels decline and the total triglyceride levels rise. The latter is presumably caused by increased cytokine concentrations (TNF α , IFN γ) and an enhanced lipogenesis in addition to impaired postprandial triglyceride clearance.

Recently, more signs and symptoms have been described in association with the lipodystrophy syndrome. Their pathogenetic relationship to fat redistribution and metabolic changes have not yet been fully evaluated. Thus, future studies need to assess whether conditions such as dry skin, ingrown toenails, aseptic hip necrosis, osteopenia and osteoporosis are linked to the lipodystrophy syndrome or are caused by independent drug or disease related effects.

HAART, Lipodystrophy Syndrome and Cardiovascular Risk

The fat redistribution and disturbances in glucose and fat metabolism resemble a clinical situation that is known as the "metabolic syndrome" in HIV-negative patients. This condition includes symptoms such as central adiposity, insulin resistance and hyperinsulinemia, hyperlipidemia (high LDL, Lp(a) hypertriglyceridemia and low HDL) and hypercoagulopathy. Given the well established cardiovascular risk resulting from this metabolic syndrome, there is growing concern about a potential therapy-related increased risk of myocardial infarction in HIV-patients. These fears are further sustained by reports of arterial hypertension on HAART, a high rate of smoking among HIV-patients and increased levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) in patients with lipodystrophy. Although many of the mainly retrospective studies dealing with this issue are inconclusive, recent data from a large international study (D:A:D study) provide evidence for an increased relative risk for myocardial infarction of 27% during the first 7 years of HAART (Friis-Møller et al. 2003). It is, however, of note that age, male gender, smoking, and pre-existing coronary artery disease were still associated with a higher risk of sustaining cardiovascular events than HAART in this study.

Several other studies used ultrasonography to measure the thickness of the carotid intima media or endothelial function to predict the cardiovascular risk. Some of these studies found abnormal test results that correlated either with the use of protease inhibitors or the presence of dyslipidemia (Currier et al. 2003). Long-term follow-up results will be necessary to substantiate these preliminary observations.

While there is some indication of an increased rate of coronary artery disease during HAART, the benefit of suppressed viral replication and improved immune function, resulting in reduced morbidity and mortality, clearly argues for the use of antiretro-

viral drugs according to current international guidelines. It seems obvious, however, that pre-existing cardiovascular risk factors in individual patients need to be considered more carefully before starting or switching HAART. Recommendations like the National Cholesterol Education Program (NECP) have been proposed for non-HIV infected patients with similar risk constellations. These guidelines are being proposed by some authors for HIV-patients as well. Clearly, more clinical studies are necessary to assess whether these recommendations are applicable in HIV-patients and to determine the clinical value of lipid lowering drug therapy in these patients. Most importantly, there is only incomplete information on the drug interactions of lipid lowering and antiretroviral drugs, based on pilot studies with limited patient numbers. The accumulation of pre-existing and drug-related risk factors will get more clinical attention because by improving the HIV-associated morbidity and mortality, HAART will increase an additional relevant cardiovascular risk factor: the age of patients who are effectively treated with antiretroviral drugs.

Pathogenesis

For a better understanding of the pathogenesis of the complex metabolic abnormalities, it is useful to separate individual aspects of the lipodystrophy syndrome: adipocytes/fat redistribution, lipid metabolism, and carbohydrate metabolism. This is because it is very likely that the lipodystrophy syndrome is not a stereotypic syndrome but rather an amalgam of miscellaneous clinical features, with perhaps multifactorial causes. Studies published during recent years provide evidence for two fundamental assumptions: firstly, lipoatrophy and lipoaccumulation result from divergent or only partially overlapping pathogenetic reasons. Secondly, NRTIs, NNRTIs, PIs, and even drugs within each class contribute to the lipodystrophy syndrome and its individual features by different, probably overlapping and certainly synergistic mechanisms.

NRTI and Lipodystrophy

The patterns of fat redistribution in patients who are exclusively receiving NRTIs are unlike those observed in patients during PI therapy. Peripheral fat loss is the major symptom observed in NRTI, although a few clinical studies describe a minimal intra-abdominal fat increase in these patients, which is clearly less than under PIs. Given that, commonly, only a mild increase in triglycerides has been observed, exclusive NRTI therapy seems to be of minor impact on lipid metabolism. Postprandially elevated FFA in patients with lipodystrophy, together with in vitro experiments, have led to the hypothesis that NRTIs could impair fatty acid binding proteins (FABP) which are responsible for cellular fat uptake and intracellular fat transport. In contrast, addition of stavudine (Zerit[®]) to a dual PI regimen did not result in a further increase in the total cholesterol or triglyceride levels.

It is well established that long-term NRTI therapy can cause mitochondrial toxicity. The clinical manifestation of this side effect presents in symptoms such as hepatic steatosis, severe hyperlactatemia, and polyneuropathy. As an explanation for these symptoms, the "pol-g hypothesis" has been proposed, which was later extended to reveal the lipoatrophy observed under NRTIs (Brinkmann et al. 1999). To maintain an adequate bioenergetic level for accurate cell function, all metabolically active cells depend on a persistent polymerase γ -mediated mitochondrial (mt) DNA synthesis. Mitochondria require a constant supply of nucleosides for this process. The mitochondrial DNA polymerase γ retains both DNA- as well as RNA-dependent DNA polymerase activity. The latter is perhaps responsible for the HIV reverse transcriptase activity and therefore its susceptibility for interactions with NRTIs.

Experimental data revealed that for the NRTI uptake into mitochondria, their subsequent phosphorylation and then incorporation into the DNA, certain pharmacodynamic requirements need to be fulfilled. These requirements, which include thymidine

kinase activity, deoxynucleotide transport specificity of the mitochondrial membrane and others, are apparently different for zidovudine (Retrovir) and stavudine (Zerit[®]), which explains the prevailing association between lipoatrophy and stavudine therapy.

The postulated mechanisms of NRTI-induced mitochondrial dysfunction consists of competitive inhibition, incorporation into the mtDNA resulting in mtDNA depletion, impairment of mitochondrial enzymes, uncoupling of oxidative phosphorylation and induction of apoptosis. Depletion of mtDNA and structural changes in the mitochondria, resulting in increased rates of apoptosis in subcutaneous adipocytes, have been confirmed by some studies. Despite the experimental link between mitochondrial toxicity and fat tissue as one potential target organ, the degree to which mitochondrial damage contributes to fat distribution abnormalities is still under debate. In contrast, mitochondrial damage is widely believed to be responsible for other NRTI-related side effects, such as myopathy, hyperlactatemia, microvesicular steatosis, and steatohepatitis with lactic acidosis.

Protease Inhibitors and Lipodystrophy

PIs account for the majority of the metabolic abnormalities of the lipodystrophy syndrome. Numerous studies report increases in the levels of total triglycerides and triglyceride-rich lipoproteins (VLDL) accompanied by raised LDL levels after initiation of PI therapy (Walli et al. 1998). Conversely, these parameters improved substantially in most studies after discontinuation of the PI or on switching to abacavir (Ziagen[®]) or nevirapine (Viramune). The hyperlipidemic changes are frequently associated with hyperinsulinemia and/or insulin resistance.

It has been proposed, based on in vitro experiments that PIs like saquinavir (Invirase[®]/Fortovase[®]), indinavir (Crixivan[®]), and ritonavir (Norvir[®]) are able to inhibit proteasomal degradation of apolipoprotein B leading to intracellular stockpiling of this lipoprotein and excessive release in response to FFA (Liang et

al. 2001). Using stable isotopes *in vivo*, other authors demonstrate a dramatic increase in FFA turnover together with increased lipolysis and decreased clearance of triglyceride-rich VLDL and chylomicrons (Shekar et al. 2002).

These conditions point towards an impaired postprandial insulin-mediated lipid metabolism since insulin normally inhibits lipolysis on the one hand and increases uptake of FFA, triglyceride synthesis, and fat oxidation in favor of glucose oxidation on the other hand. It remains unclear so far whether impaired insulin action eventually leads to dyslipidemia or whether hyperlipidemia is responsible for reduced insulin function and insulin resistance in the periphery. Presumably both mechanisms are important given that some PIs (e.g. indinavir) have been shown to induce insulin resistance without changes occurring in lipid metabolism after short-term administration (Noor et al. 2001, Noor et al. 2002), whereas other PIs (e.g. ritonavir) have been demonstrated to cause mainly hyperlipidemia without major changes occurring in glucose metabolism (Purnell et al. 2000). However, comparative clinical studies, regarding the association of the different PIs with insulin resistance, are still lacking.

It is reasonable to speculate that lipid abnormalities, and in particular increased FFA levels, contribute substantially to the peripheral and central insulin resistance of skeletal muscles and the liver, presumably due to the increased storage of lipids in these organs (Gan et al. 2002). Given this hypothesis, the visceral adiposity could reflect the adaptation of the body in response to raised FFA concentrations and an attempt to minimize the lipotoxic damage to other organs.

Several *in vitro* experiments have indicated that almost all PIs can potentially lead to insulin resistance in adipocytes. Short-term administration of indinavir caused an acute and reversible state of peripheral insulin resistance in healthy volunteers, which was determined in an euglycemic-hyperinsulinemic clamp. These effects are most likely caused by the inhibition of glucose transport mediated by GLUT-4, the predominant trans-

porter involved in insulin-stimulated cellular glucose uptake in humans (Murata et al. 2002). In some patients with lipodystrophy, additional impairment of glucose phosphorylation may contribute to the insulin resistance (Behrens et al. 2002). This is presumably due to an impaired insulin-mediated suppression of lipolysis and subsequently increased FFA levels (Behrens et al. 2002, van der Valk et al. 2001). Peripheral insulin resistance may also account for an increase in the resting energy expenditure in HIV-lipodystrophy and a blunted insulin-mediated thermogenesis.

Indinavir may also induce insulin resistance by inhibiting the translocation, processing or phosphorylation of the sterol regulatory element-binding protein 1c (SREBP-1c) (Caron et al. 2001, Bastard et al. 2002). SREBP-1, either directly or via the peroxisome proliferator activated receptor γ (PPAR γ), regulates FFA uptake and synthesis, adipocyte differentiation and maturation, and glucose uptake by adipocytes. Similarly, the function of these factors have been proposed to be disturbed in inherited forms of lipodystrophies.

Diagnosis

Both lack of a formal definition and uncertainty about the pathogenesis and possible long-term consequences, leads to a continuing discussion about appropriate guidelines for the assessment and management of the HIV-lipodystrophy syndrome and its metabolic abnormalities. Outside clinical studies, the diagnosis relies principally on the occurrence of apparent clinical signs and their reporting by the patient. This appears sufficient for the routine clinical assessment especially when the body habitus changes develop rather rapidly and severely. For clinical investigations however, especially in epidemiologic and intervention studies, more reliable measurements are required. But, at this time, no technique has demonstrated sufficient sensitivity, specificity or predictive value to definitively diagnose the HIV-lipodystrophy syndrome by comparison with results

obtained from a "normal" population. A definition proposed by Carr et al. (1999) has been frequently used so far (Table 1). A recent multicenter study to develop an objective and broadly applicable case definition proposes a model including age, sex, duration of HIV infection, HIV disease stage, waist to hip ratio, anion gap, serum HDL cholesterol, trunk to peripheral fat ratio, percentage leg fat, and intra-abdominal to extra-abdominal fat ratio. Using these parameters, the diagnosis of lipodystrophy had a 79% sensitivity and 80% specificity. Although this model is largely for research and contains detailed body composition data, alternative models and scoring systems, incorporating only clinical and metabolic data, also gave reasonable results (for more information see <http://www.med.unsw.edu.au/nchechr>).

Table 1. Possible signs and symptoms of the HIV-associated lipodystrophy syndrome

(according to Carr et al. 1999) All list requirements from A to D must be fulfilled; at least one condition of A and B must be present.

A	One or more symptoms (patient report, physical examination) occurring since the initiation of HAART: 1. Peripheral subcutaneous fat loss (face, arms, legs) 2. Central adiposity (abdomen, dorsocervical fat pads, increased breast size in women)
B	One or more metabolic changes since starting HAART: 1. Fasting triglycerides >200 mg/dl (5,3 mmol/l) 2. Fasting cholesterol >200 mg/dl (2,2 mmol/l) 3. Fasting C-peptide >7,5 ng/ml (2,5nmol/l) 4. Impaired glucose metabolism – Impaired fasting glucose 110-126 mg/dl (6,1-7,0 mmol/l) – Impaired glucose tolerance 140-200 mg/dl (7,8-11,1 mmol/l) – Diabetes mellitus: fasting glucose $\geq$ 126 mg/dl (7,0 mmol/l, 2-hour glucose $\geq$ 200 mg/dl (11,1 mmol/l) 5. Hyperlactatemia > 2,1 mmol/l
C	No active AIDS-defining or other severe illness during last 3 months
D	No current steroid therapy or treatment with immunomodulators

Despite individual limitations, several techniques are suitable for measuring regional fat distribution. These include dual energy x-ray absorptiometry (DEXA), computer tomography (CT), magnetic resonance imaging (MRI) and sonography. Anthropometric measurements are safe, portable, cheap and much easier to perform than imaging techniques. Waist circumference alone, as well as sagittal diameter, are more sensitive and specific measures than waist-to-hip ratio. Repeated measurements of skin fold thickness can be useful for individual long-term monitoring but need to be performed by an experienced person.

The main imaging techniques (MRI, CT, DEXA) differentiate tissues on the basis of density. Single-slice measurements of the abdomen and extremities (subcutaneous adipose tissue = SAT, visceral adipose tissue = VAT) and more complex three-dimensional reconstructions have been used to calculate regional or total body fat. Limitations of these methods include most notably their expense, availability and radiation exposure (CT). Consequently, CT and MRI should be considered in routine clinical practice only for selected patients (e.g. extended dorsocervical fat pads, differential diagnosis of non-benign processes and infections). DEXA is appropriate for examining appendicular fat, which is comprised almost entirely of SAT and has been successfully employed in epidemiologic studies. However, SAT and VAT cannot be distinguished by DEXA, which therefore limits the evaluation of changes in truncal fat. Application of sonography to measure specific adipose compartments, including those in the face, requires experienced investigators and has been minimally applied in HIV infection so far. Bioelectrical impedance analysis estimates the whole body composition and cannot be recommended for measurement of abnormal fat distribution.

Patients should routinely be questioned and examined for cardiovascular risk factors, such as smoking, hypertension, adiposity, type 2 diabetes, and family history. For a valuable assessment of blood lipid levels it is recommended to obtain

blood after a fasting of at least 8 hours. Total cholesterol and triglycerides together with LDL and HDL cholesterol should be obtained prior to the initiation of, or a switch to, a new potent antiretroviral therapy and repeated 3 to 6 months after starting or switching therapy. Fasting glucose should be assessed with at least a similar frequency. The oral glucose tolerance test (OGTT) is a reliable and accurate instrument to evaluate insulin resistance and glucose intolerance. An OGTT may be indicated in patients with suspected insulin resistance like those with adiposity ($\text{BMI} > 27 \text{ kg/m}^2$), a history of gestational diabetes and a fasting glucose level between 110 to 126 mg/dl (impaired fasting glucose). An intravenous glucose tolerance test or hyperinsulinemic-euglycemic clamp appears only feasible in clinical studies. The diagnosis of diabetes is based on fasting glucose levels $> 126 \text{ mg/dl}$, glucose levels of $> 200 \text{ mg/dl}$ independent of fasting status or a 2-hour OGTT glucose level above 200 mg/dl. Additional factors that could lead to or assist in the development of hyperlipidemia and/or insulin resistance always need to be considered (e.g. alcohol consumption, thyroid dysfunction, liver and kidney disease, hypogonadism, concurrent medication like steroids, β -receptor blockers, thiazides etc.)

Therapy

So far, most attempts to improve or even reverse the abnormal fat distribution by modification of the antiretroviral treatment, have shown only modest success. In particular, peripheral fat loss appears to be resistant to most therapeutic interventions. The metabolic components of the syndrome may be easier to improve (Table 2).

Table 2. Therapeutic options for HIV-associated lipodystrophy and related metabolic complications

Lifestyle changes (reduce saturated fat and cholesterol intake, increase physical activity, cessation of smoking);
Change antiretroviral therapy [replacement of PI, replacement of stavudine (Zerit [®])]
Statins [e.g. Atorvastatin (Sortis [®]) Pravastatin (Pravasin [®])]
Fibrates [e.g. Gemfibrozil (Gevilon [®]) or Bezafibrat (Cedur [®])]
Metformin (e.g. Glucophage [®])
Recombinant humane growth hormones (e.g. Serostim [®])
Surgical intervention

The clinical benefit, however, of lipid lowering or insulin-sensitizing therapy in HIV patients with lipodystrophy remains to be demonstrated. In light of the potentially increased cardiovascular risk to antiretroviral therapy recipients, an American AIDS clinical trial group (ACTG) published recommendations based on the National Cholesterol Education Program (NCEP) for primary and secondary prevention of coronary artery disease in seronegative patients (Table 3). In addition, more detailed recommendations by an International AIDS Society-USA Panel have been published to provide guidelines for physicians actively involved in HIV care. However, these recommendations should be considered as being rather preliminary, given the so far limited number, size and duration of the clinical studies they are based on.

Table 3. Preliminary therapy recommendations for HAART-associated hyperlipidemias

Risk Category	Recommendations		
	„aimed“ LDL	diet if LDL	Lipid-lowering drugs if LDL
No diabetes, no CHD			
< 2 RF	< 160 mg/dl	≥ 160 mg/dl	≥ 190 mg/dl
≥ 2 RF	< 130 mg/dl	≥ 130 mg/dl	≥ 160 mg/dl
CHD	< 100 mg/dl	≥ 100 mg/dl	≥ 130 mg/dl
Diabetes mellitus			
No CHD, no RF	< 100 mg/dl	> 100 mg/dl	≥ 130 mg/dl
CHD or RF	< 100 mg/dl	> 100 mg/dl	> 100 mg/dl

CHD: coronary heart disease, RF: risk factors for CHD.

Age (male ≥ 45 years, female ≥ 55 years or premature menopause without hormone replacement, positive family history for premature CHD (in first-degree relatives <55 years and first-degree female relatives <65 years), cigarette smoking, hypertension (blood pressure ≥ 140/90 mm Hg or taking antihypertension drugs), HDL <40 mg/dl (1.0 mmol/l). If HDL cholesterol is over >60 mg/dl (1.6 mmol/l), subtract one risk factor from the total (adapted from Dubé et al. 2000 and Schambelan et al. 2002)

Lifestyle Changes

Dietary interventions are commonly accepted as the first therapeutic option for hyperlipidemia, especially hypertriglyceridemia. Whenever possible, dietary restriction of the total fat intake to 25-35% of the total caloric intake should be a part of the treatment in conjunction with lipid-lowering drugs. Consideration should be given to consulting professional and experienced dieticians for HIV-infected patients and their partners. Patients with excessive hypertriglyceridemia (>1000 mg/dl) may benefit from a very low-fat diet and alcohol abstinence to reduce the risk of pancreatitis, especially if there is a positive family history or concurrent medications that may harbor a risk of developing pancreatitis. Regular exercise may have beneficial effects, not only on triglycerides and insulin resistance, but probably also on fat redistribution, and should be considered in all HIV-infected patients. All patients should be advised and

supported to cease smoking in order to reduce the cardiovascular risk.

Specific Interventions

Given the extensive indications that PIs are the culprits substantially contributing to the metabolic side effects, numerous attempts have tried to substitute the PI component of a regimen with nevirapine, efavirenz, or abacavir. Indeed, these "switch-studies" have demonstrated substantial improvement, although not normalization, of serum lipids and/or insulin resistance in many patients. However, the lipodystrophic changes failed to improve clinically even if imaging techniques revealed some minor recovery. Under restricted inclusion criteria and study conditions, most patients maintained complete viral suppression after changes to the HAART, but not all of these studies included control groups with unchanged antiretroviral therapy. The most advantageous changes of metabolic parameters have been observed after replacement of the PI by nevirapine or abacavir. This option is however not always suitable, and the clinical benefit of effective viral suppression and improved immune function needs to be considered in view of the drug history, current viral load, and resistance mutations. When options are limited, antiretroviral drugs that may lead to lipid elevations should not be withheld for fear of further exacerbating lipid disorders.

Lipid lowering agents should be considered for the treatment of severe hypertriglyceridemia, elevated LDL or a combination of both. HMG-CoA reductase inhibitors have been successfully used in combination with dietary changes in HIV patients with increased total and LDL cholesterol. Many of the statins (as well as itraconazole, erythromycin, diltiazem etc.) share common metabolism pathways with PIs via the cytochrome P450 3A4 system, thereby potentially leading to additional side effects due to increased plasma levels of statins which can then cause liver and muscle toxicity. Based on limited pharmacokinetic and clinical studies, atorvastatin (Sortis[®]) and pravastatin (Pravasin[®]), administered at 20-40 mg once daily, are the pre-

ferred agents for a carefully monitored therapy in HIV-infected patients on HAART. Lovastatin (Mevinacor[®]) and simvastatin (Zocor[®]) should be avoided due to their potential interaction with PIs.

Fibric acid analogues like gemfibrozil or fenofibrate are particularly effective in reducing the triglyceride levels and should be considered in patients with severe hypertriglyceridemia (>1000 mg/dl). Fibric acid analogues retain a supportive effect on lipoprotein lipase activity and can thereby lower LDL levels. Despite their potentially synergistic effect, co-administration of fibric acid analogues and statins in patients on HAART should only be used carefully in selected patients, since both can cause rhabdomyolysis. In addition, it is rational to start therapy with a statin, followed by the addition of the fibric acid analogue after four months if the response is suboptimal and demands further treatment intensification. Niacin acid has been shown to only minimally improve the hyperlipidemia induced by HAART but increases the peripheral insulin resistance and is therefore currently not recommended for HIV patients receiving HAART. Finally, it should be stressed that the long-term effects of lipid-lowering agents and their impact on cardiovascular outcomes, especially in HIV-patients with moderate or severe hypertriglyceridemia, are unknown.

Metformin has been evaluated for the treatment of the lipodystrophy syndrome. Some studies revealed a positive effect on the parameters of insulin resistance and the potential reduction of intra-abdominal (but also subcutaneous) fat, although not clinically obvious. Thiazolidinediones, such as rosiglitazone (Avandia[®]) or pioglitazone (Actos[®]), exhibit the potency to improve insulin sensitivity via stimulation of the PPAR γ and other mechanisms. Rosiglitazone has been successfully used to treat abnormal fat distribution in genetic lipodystrophies. Preliminary studies in HIV patients, however, revealed only a minimal improvement in the abnormal fat distribution but an increase in insulin sensitivity.

Recombinant growth hormone (e.g. Serostim[®]) at doses of 6 mg/d s.c. over a time course of 8-12 weeks has been demonstrated in some small studies to be a successful intervention for reducing visceral fat accumulation. Unfortunately, these improvements have been shown to consistently reverse the discontinuation of growth hormone therapy. Studies with lower maintenance doses have not been performed yet. The possible side effects associated with growth hormone therapy include arthralgia, peripheral edema, insulin resistance and hyperglycemia.

Surgical intervention (liposuction) for the treatment of local fat hypertrophy has been successfully performed but appears to be associated with an increased risk of secondary infection, and recurrence of fat accumulation is possible. For the treatment of facial lipoatrophy, subcutaneous injection of poly-L-lactic acid and autologous fat has been effectively used in a limited number of HIV-patients (Valantin et al. 2003, Lafaurie M et al. 2003). Further evaluation in long-term follow-up studies is necessary to fully assess the value of these methods.

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Chapter 6: HIV Resistance Testing

Eva Wolf

The development of resistant viral strains is one of the main reasons for failure of antiretroviral therapy. If there is resistance to several drug classes, the number of alternative treatment regimens is limited and the virological success of subsequent therapies, or so-called salvage regimens, may be only short-lived.

The rapid development of resistant variants is due to the high turnover of HIV – approximately 10 million new viral particles are produced every day(!) (Perelson et al. 1996) – and the exceptionally high error rate of HIV reverse transcriptase. This leads to a high mutation rate and constant production of new viral strains, even in the absence of treatment. In the presence of antiretroviral drugs, resistant strains are selected as the dominant species (Drake et al. 1993).

Assays for Resistance Testing

There are two established assays for measuring resistance or sensitivity of HIV to antiretroviral drugs – the genotypic and the phenotypic resistance tests.

Both assays are available commercially (genotypic resistance tests: e.g. HIV-1 TrueGene™, *Visible Genetics*; ViroSeq™; *Applied Biosystems*; ViroGene™ *LabCorp/Virco*; GenoSure™, *LabCorp*; GENChec™, *Virco*; GeneSeq™, *Virologic*; InnoLipa®, *Bayer*; phenotypic resistance tests: e.g. Antivirogram®, *Virco*; PhenoSense™, *ViroLogic*; Phenoscript™, *VIRalliance*).

The total cost – depending on the assay and laboratory used – ranges from 350 to 500 Euro for genotyping, and is approximately twice as high for phenotyping.

The problem with both methods is that a minimal amount of virus is necessary to perform the test. A viral load below 500-1000 copies/ml often does not allow detection of resistance.

Phenotyping

Phenotypic resistance tests involve direct quantification of drug sensitivity.

Viral replication is measured in cell cultures under the selective pressure of increasing concentrations of antiretroviral drugs and is compared to the wild-type.

Drug concentrations are expressed as IC_{50} values (50 % inhibitory concentration). The IC_{50} is the concentration of drug that is required to inhibit viral replication by 50 %. The sensitivity of the virus is expressed as the IC_{50} compared with the so-called cut-off value. The cut-off value indicates by which factor the IC_{50} of an HIV isolate can be increased in comparison to the wild-type, whilst still being classified as sensitive. Determination of the cut-off is crucial for the interpretation of results!

Currently, three different cut-offs are being used. The *technical cut-off* is a measure for the methodological variability of the assay and is approximately 2.5 fold more than the IC_{50} . The *biological cut-off*, for example the comparative value on an antivirogram, includes the inter-individual variability of virus isolates from ART-naïve HIV patients, and is slightly higher than the technical cut-off. The biological cut-off does not, however, allow prediction of the clinical response to a drug. The *clinical cut-off* indicates up to which levels of IC_{50} virological success can still be expected.

Disadvantages of phenotypic testing include the lengthy procedure and high expense of the assay.

Genotyping

Genotypic assays are based on the analysis of mutations associated with resistance. These are determined by the direct sequencing of the amplified HIV genome or by specific hybridi-

zation techniques with wild-type or mutant oligonucleotides. Genotype tests only detect viral mutants comprising at least 20 to 30 % of the total population and provide an indirect measurement of drug resistance. Mutations that are associated with reduced sensitivity have been well-described for most HIV drugs, but the high number of different resistance patterns, which may also contain compensatory mutations, make the determination of the degree of resistance to particular drugs difficult.

The analysis of genotypic resistance patterns is based on the correlation between the genotype and the phenotype. There is data available from *in vitro* studies, clinical observations and duplicate testing, in which genotypically localized mutations were investigated for phenotypic resistance.

Some of the most important databases for resistance profiles and interpretational systems are freely available on the following websites:

Stanford-Database: <http://hiv.net/link.php?id=24>

Los Alamos-Database: <http://hiv.net/link.php?id=25>

geno2pheno (Arevir): <http://hiv.net/link.php?id=26>.

The commercial suppliers of resistance tests also provide guidelines for interpretation in their systems (e.g. VirtualPhenotype™, *Virco*; TruGene™, *Visible Genetics*; Retrogram™, *Virology Networks*).

The discussion about genotypic resistance in this chapter is limited to the sequencing of reverse transcriptase and protease and to the patterns of resistance that emerge on treatment.

Background

Within the nucleotide sequences of the HIV genome, a group of three nucleotides, called a codon, defines a particular amino acid in the protein sequence. Resistance mutations are described using a number, which shows the position of the relevant codon, and two letters. The letter preceding the number corre-

sponds to the amino acid specified by the codon at this position in the wild-type virus. The letter after the number describes the amino acid that is produced from the mutated codon.

Mechanisms of Resistance

NRTIs: Nucleoside and nucleotide analogs (NRTIs) are pro-drugs and only become effective after being converted to triphosphates. Nucleotide analogs require only two instead of three phosphorylation steps. Phosphorylated NRTIs compete with naturally occurring dNTPs (desoxynucleotide triphosphates). The incorporation of a phosphorylated NRTI into the proviral DNA blocks further elongation of the proviral DNA and leads to interruption of the chain.

There are two main biochemical mechanisms that lead to NRTI resistance (De Mendoza et al. 2002). *Sterical inhibition* is caused by mutations enabling the reverse transcriptase to recognize structural differences between NRTIs and dNTPs. Incorporation of NRTIs is then prevented in favor of dNTPs (e.g. with the M184V mutation; Naeger 2001). *Phosphorylysis* via ATP (adenosine triphosphate) or pyrophosphate leads to removal of the already incorporated NRTIs from the growing DNA chain. This is the case with the following mutations: M41L, D67N, K70R, L210W, T215Y and K219Q (Meyer et al. 2000). Phosphorylysis leads to cross-resistance between NRTIs, the degree of which may differ between substances (AZT, d4T > ABC > ddC, ddI > 3TC).

PIs: PI resistance usually develops slowly, as several mutations must accumulate. This is also referred to as the genetic barrier. For PIs, a distinction is made between *primary* and *secondary mutations*. *Primary mutations* are located within the active site of the target enzyme, the HIV protease, and reduce the ability of the protease inhibitor to bind to the enzyme. Primary mutations may also lead to reduced activity of the protease. *Secondary mutations* are located outside of the active site and usually occur after primary mutations, resulting in phenotypic resistance. They compensate for the reduction in viral fitness caused by

primary mutations. However, differentiation of primary and secondary mutations can only provide an approximate estimation of the degree of resistance.

Transmission of Resistant HIV Strains

The clinical relevance of mutations that are already present at the initiation of treatment is still unclear. In a retrospective study of 115 patients, no phenotypic PI resistance was found. Phenotypic NNRTI resistance for nevirapine was found in 10 % of patients, for delavirdine in 25 % and for efavirenz in 4 %. Less than 1 % of patients had phenotypic resistance to NRTIs. 13 % of patients received an antiviral drug within the initial regimen which had a reduced activity (Miller et al. 1999a). The anticipated negative effect of pre-existing mutations on the success of treatment in ART-naïve patients could not be confirmed in a retrospective study on 34 seroconverted patients (Balotta et al. 1999).

Clinical Studies

The clinical relevance of resistance testing before therapy is changed has been shown in several prospective, controlled studies, both for genotypic (Durant et al. 1999, Baxter et al. 1999, Tural et al. 2001) and phenotypic resistance testing (Cohen et al. 2000). Patients whose treating physicians received information on the existing mutations before the therapy was changed usually had more significant decreases in the viral load than patients in whom treatment was changed without knowledge of the resistance profile.

Interpretation of Genotypic Resistance Profiles

NRTIs

For several NRTIs, such as lamivudine, and for NNRTIs, a high degree of resistance can develop with only a single mutation

(Havlir et al. 1996, Schuurman et al. 1995). For this reason, such drugs should only be used in highly effective regimens. However, in a retrospective analysis of five large studies the overall outcome of treatment was not proven to be inferior in the presence of the lamivudine-specific M184V mutation. The reason for this could be that the M184V mutation leads to reduced viral replication and reduced viral fitness (Sharma et al. 1999). On lamivudine monotherapy, after 52 weeks the viral load remained 0.5 log below the initial levels despite early development of the M184V mutation (Eron et al. 1995).

The term "TAMs" – thymidine analog mutations – is relatively new. TAMs include the mutations M41L, D67N, K70R, L210W, T215Y and K219Q, which were initially observed on zidovudine therapy (Larder et al. 1989). It is now known that these mutations can also be selected by stavudine (Loveday et al. 1999). Three or more TAMs are associated with a relevant reduction in the sensitivity to stavudine (Shulman et al. 2001). The term "NAMs" (nucleoside analog mutations) is also used instead of TAMs, as these mutations are associated with cross-resistance to all other nucleoside analogs, with the exception of lamivudine.

Viral mutants, isolated from patients in whom treatment on zidovudine, lamivudine or abacavir has failed, usually have a measurable phenotypic resistance. Two TAMs result in a 5.5-fold, three NAMs in a 29-fold and four NAMs or more in a >100-fold reduced sensitivity to zidovudine. The use of abacavir in cases of more than a 7-fold reduction in sensitivity no longer promises success. This usually requires at least 3 NAMs in addition to the M184V mutation (Harrigan et al. 2000).

The development of a measurable phenotypic resistance to stavudine or didanosine has been observed less frequently, and has been more moderate in character (Larder et al. 2001). The clinical cut-off for stavudine and didanosine presumably lies below the technical cut-off. Phenotypic resistance is therefore not measurable, at least in part. Clinical data indicates that tenofovir is effective even in the presence of NAMs such as D67, K70R,

T215Y/F or K219Q/E. However, if three or more NAMs include M41L or L210W, a reduced virological response can be expected (Drug Resistance Mutations Group of the IAS-USA 2001).

M184V, the lamivudine-associated mutation, as well as the L74V mutation, observed on didanosine treatment, and the NNRTI-specific mutations, L100I and Y181C, may have an antagonistic effect on the development of resistance (Vandamme et al. 1999).

M184V induces resensitization to zidovudine and stavudine, providing that there are no more than three other zidovudine- or stavudine-associated mutations present (Shafer 1995, Naeger et al. 2001). In one genotypic and phenotypic resistance study consisting of 9,000 samples, 94 % of cases with M184V had a more than 10-fold increase in lamivudine resistance. A combination of M41L, L210W and T215Y increased the resistance to zidovudine by more than 10-fold in 79 % of cases. If the M184V mutation was also present, only 52 % had a more than 10-fold increase in zidovudine resistance (Larder et al. 1999a). The M184V mutation also increases the sensitivity to tenofovir (Miller et al. 2001). In contrast to this, the presence of M184V plus multiple NAMs or mutations at positions 65, 74 or 115 increased the resistance to didanosine, zalcitabine and abacavir (Harrigan et al. 2000, Lanier et al. 2001).

So-called multidrug resistance (MDR) to all nucleoside analogs – except lamivudine – is established if one of the following combinations occurs: T69SSX, i.e. the T69S mutation plus an insertion of 2 amino acids (SS, SG or SA) between positions 69 and 70, plus a zidovudine-associated mutation or Q151M, plus a further MDR mutation (V75I, F77L or F116; Masquelier et al. 2001).

The MDR mutation, Q151M, alone leads to intermediate resistance to zidovudine, stavudine, didanosine, zalcitabine and abacavir (Shafer 2002a). It is relatively uncommon, with a prevalence of below 5 %. In contrast, Q151M does not lead to the

loss of activity of tenofovir. Instead, the T69S insertion induces an approximately 20-fold increase in the resistance to tenofovir (Miller et al. 2001).

The L74V mutation emerges on didanosine or abacavir and leads to a 2-5 fold increase in the resistance to didanosine or zalcitabine (Winters et al. 1997). The loss of efficacy, by a factor of around 2-3, for abacavir is not considered clinically relevant and requires further mutations (Tisdale et al. 1997).

The K65R mutation leads to an intermediate resistance to didanosine, abacavir, zalcitabine, lamivudine and tenofovir (Shafer 2002a) as well as to reduced viral fitness.

The V75T mutation, which is associated with an approximately 5-fold increase in the resistance to stavudine, didanosine and zalcitabine, is only rarely observed (Lacey et al. 1994).

In large patient cohorts, quantitative measurements of sensitivity have shown that up to 29 % of NRTI-experienced patients have a hypersusceptibility to NNRTIs (i.e. a reduction in the inhibitory concentration by a factor of 0.3-0.6). A reduction in the zidovudine or lamivudine sensitivity correlated with an increased NNRTI susceptibility (Whitcomb et al. 2000). However, these results have not influenced treatment strategies so far.

NNRTIs

A single mutation can confer a high degree of resistance to one or more NNRTIs. The relatively frequent K103N mutation leads to a 20-30-fold increase in resistance to all available NNRTIs (Petropoulos et al. 2000). Further use of NNRTIs in the presence of this mutation is therefore not recommended.

V106A leads to a 30-fold increase in nevirapine resistance and intermediate efavirenz resistance. A98G, K101E and V108 lead to low-grade resistance to all available NNRTIs. Intermediate resistance to efavirenz and delavirdine and low-grade resistance to nevirapine result from the L101I mutation. Y181C/I causes a 30-fold increase in nevirapine resistance and only a temporary

response to efavirenz. G190A is associated with a high degree of nevirapine resistance and an intermediate resistance to efavirenz and delavirdine. G190S and Y188C/L/H are mutations resulting in a high degree of nevirapine and efavirenz resistance (Shafer 2002b, De Mendoza et al. 2002).

PIs

The spectrum of PI mutations has been well described. Although there is a high degree of cross-resistance between saquinavir, nelfinavir, indinavir and ritonavir, the primary mutations are relatively specific for the individual drugs. If treatment is changed early on to another PI combination, i.e. before the accumulation of several mutations, the subsequent regimen may still be successful.

Polymorphisms at positions 10, 20, 36, 63, 71, 77 and 93 do not lead to resistance per se, but compensate for the reduced protease activity caused by primary mutations (Nijhuis et al. 1999).

The typical nelfinavir-specific resistance profile with the D30N primary mutation and further secondary mutations resulted in only a low degree of cross-resistance to indinavir, ritonavir or saquinavir (Larder et al. 1999a). If the M46I, V82A and L90M mutations and several further secondary mutations were present, samples were shown to be resistant to ritonavir in 77 %, to nelfinavir in 73 %, indinavir in 53 % and saquinavir in 45 % of cases. A retrospective analysis of treatment failure in the NV15436 study demonstrated that the L90M mutation was associated both with saquinavir and nelfinavir resistance (Craig et al. 1999).

A comparison of the replicative capacity of a virus with a single protease mutation, D30N or L90M, with the wild-type virus demonstrated a significant loss of viral fitness in the presence of the D30N mutation selected by nelfinavir. In contrast, the L90M mutation, which is triggered by saquinavir, only leads to a moderate reduction in the replicative capacity, which can be compensated by the frequently occurring L63P polymorphism.

Conversely, the L63P mutation hardly influences the reduced replicative capacity of D30N mutants (Martines et al. 1999).

G48V mainly emerges on saquinavir and leads to 10-fold increase in the resistance to saquinavir – in combination with L90M it results in a high degree, over 100-fold, resistance to saquinavir (Jakobson et al. 1995).

V82A(/T/F/S) occurs mainly on indinavir and/or ritonavir – and, in combination with other mutations, leads to cross-resistance to other PIs (Shafer 2002c).

Mutations that frequently develop on indinavir, such as M46I/L63P/V82T/I84V or L10R/M46I/L63P/V82T/I84V are just as fit as the wild-type.

The I84V mutation leads to clinical resistance to all PIs (Kempf et al. 2001).

The resistance pattern of amprenavir is different to that of other PIs. Amprenavir most frequently leads to the I50V, I54L or I54M, mutations, which are associated with reduced sensitivity to all PIs, but particularly to amprenavir (Snowden et al. 2000). In a study of 132 patients with a partly extensive PI-experience, 71 % with a >2-fold reduction in sensitivity to 1-3 PIs and 37 % of samples with a reduced sensitivity to 4 PIs were still sensitive to amprenavir. The L10I/R/V/F, M46I/L, I54L/V, I84V and L90M mutations were significantly associated with amprenavir resistance (Schmidt et al. 2000).

No specific mutations have been described for lopinavir to date. However, mutations at positions 10, 20, 24, 46, 53, 54, 63, 71, 82, 84, 90 are associated with a reduced sensitivity as with all other PIs (Kempf et al. 2001). In particular, the K20M/R and F53L mutations in combination with several other mutations led to a significant reduction in sensitivity.

Response in PI-experienced patients correlates with the number of mutations present. With up to 5 mutations, the IC_{50} is increased by a median factor of 2.7, for 6-7 mutations by a factor of 13.5 and with at least 8 mutations by a factor of 44. However, lopinavir still seems to have good efficacy despite some

cross-resistance to indinavir, ritonavir, saquinavir and nelfinavir. In a group of PI-experienced patients, 63 % showed a reduction in sensitivity to the previous PI by at least a factor of 4, only 5 % showed a significant reduction in the phenotypic susceptibility to lopinavir. Even the presence of resistance mutations such as L10I/R, I54V, A71V/T, V82A/F/T, which are associated with reduced lopinavir susceptibility, did not correlate with lower efficacy after 6 or 12 months. This good efficacy is due to the high plasma levels of lopinavir in combination with ritonavir, which – for the wild-type virus – are >30-fold above the EC₅₀-concentration during the entire dose interval and – in this case – still exceed the EC₅₀-concentration by a factor of at least 12 (Kempf et al. 2000).

New Drugs

The following chapter describes the resistance profiles of several newly developed antiretroviral drugs.

AG1549 (capravirine), a second generation NNRTI. Seems to have activity even in the presence of Y181C, which is associated with loss of sensitivity to nevirapine and delavirdine, or the NNRTI mutation K103N, which confers resistance to all currently available NNRTIs (Dezube et al. 1999, Potts et al. 1999).

TMC 125, a second generation NNRTI, which is effective against both wild-type viruses and viruses with NNRTI mutations such as L100I, K103N, Y181C, Y188L and/or G190A/S (Gazzard et al. 2002).

DPC083, another second generation NNRTI with a good pharmacokinetic profile. It is effective against single mutations such as K100I or K103N, as well as in the presence of the double mutations K103N + Y181C, K103N + V108I or K103N + P225H, which are observed in failure of nevirapine, delavirdine and efavirenz therapy (Fiske et al. 2000).

Tipranavir (TPV), the first non-peptide protease inhibitor, which shows good efficacy against PI-resistant viruses. In phenotypic resistance testing, 90 % of isolates with a high degree

of resistance to ritonavir, saquinavir, indinavir and nelfinavir were still sensitive to tipranavir (Larder et al. 2000). In a study of 41 patients, pre-treated with at least two PIs, TPV/RTV-treatment remained effective after 48 weeks in 35 patients. A more than 10-fold increase in tipranavir resistance occurred in only one patient. The number and type of PI mutations before initiation of TPV/RTV were not associated with the virological response. In four out of six isolates with reduced susceptibility, the point mutations V82T and L33 (I, F, or V) occurred (Schwartz et al. 2002).

There is only limited data available on the resistance profile of atazanavir (*Reyataz*®), a new azapeptide PI. There is presumably partial cross-resistance with other PIs – 30-67 % of virus isolates with reduced sensitivity to 3-4 PIs were also less sensitive to atazanavir (Colonno 2000). The primary atazanavir mutation seems to be at position 88 (N88S; Gong et al. 2000). In treatment-naïve patients, treated with atazanavir, the development of the I50L mutation – frequently in combination with A71V – led to a reduction in the sensitivity to atazanavir, but also to an increased sensitivity to amprenavir, indinavir, nelfinavir, ritonavir and saquinavir (Colonno et al. 2002).

In PI-experienced patients, the accumulation of further PI mutations, in particular I84V, simultaneously leads to a further reduction in sensitivity to other PIs.

Summary

Controlled studies show that resistance testing improves antiretroviral treatment in HIV patients. Although HIV treatment guidelines generally recommend resistance testing, and the first pharmaco-economic studies show that these tests may even be cost effective (Weinstein et al. 2001), resistance tests are still not covered by the public health insurance in many countries.

Currently, both genotypic and phenotypic tests show good intra- and inter-assay reliability. However, the interpretation of resistance profiles has become very complex and requires a constant

updating of the guidelines. The determination of the thresholds associated with clinically relevant phenotypic drug resistance is crucial for the effective use of phenotypic testing.

Even if treatment failure requires the consideration of other causal factors, such as compliance of the patient, metabolism of drugs and drug levels, resistance testing is of great importance in antiretroviral therapy.

Resistance Tables

Table 1: Mutations leading to RTI resistance (modified from ANRS – AC 11 Groupe Resistance, Sept. 2002, <http://hiv.net/link.php?id=138> and De Mendoza 2002, Shafer 2002a-c, Drug Resistance Mutations Group of the International AIDS Society-USA 2001)

RTI	Resistance mutations
Zidovudine	T215 Y/F (esp. with other TAMs*) ≥ 3 of the following mutations: M41L, D67N, K70R, L210W, K219Q/E Q151M (esp. with A62V/F77L/F116Y) T 69 SSX (insertion)**
Stavudine	V75M/S/A/T T215Y/F (usually in combination with other TAMs*) ≥ 3 TAMs* Q151M (esp. with A62V/F77L/F116Y) T 69 SSX (insertion)**
Abacavir	≥ 5 of the following mutations M41L, D67N, L74V, M184V, L210W T215Y/F M184V+L74V+/-115F +/-K65R Q151M (esp. with A62V/F77L/F116Y) T 69 SSX (insertion)**
Lamivudine	M184V/I T 69 SSX (insertion)**
Didanosine	L74V T215 Y/F und ≥ 3 of the following mutations: M41L, D67N, K70R, L210W, K219Q/E Q151M (esp. with A62V/F77L/F116Y) T 69 SSX (insertion)** K65R (partial resistance) M184V (partial resistance)
Zalcitabine	T69D/N/S L74V Q151M (esp. with A62V/F77L/F116Y) T 69 SSX (insertion)** K65R (partial resistance) M184V (partial resistance)
Tenofovir DF	T 69 SSX (insertion)** ≥ 3 TAMs with M41L or L210W K65R (partial resistance)

*TAMs = thymidine analog mutations

** T69 SSX in combination with T215Y/F and other TAMs leads to a high degree of resistance to all NRTIs and tenofovir

Table 2: Mutations leading to NNRTI resistance (modified from ANRS – AC 11 Groupe Resistance, Sept. 2002, <http://hiv.net/link.php?id=138> and De Mendoza 2002, Shafer 2002a-c, Drug Resistance Mutations Group of the International AIDS Society-USA 2001).

Mutations associated with a high degree of resistance in **bold font**.

NNRTIs	Resistance mutations
Efavirenz	L100I
	K101E
	K103N
	Y181C
	Y188L
	G190S/A
	P225H
	M230L
Nevirapine	A98G
	L100I
	K101E
	K103N
	V106A
	Y181C/I
	Y188C/H
	G190A/S
Delavirdine	M230L
	A98G
	L100I
	K101E
	K103N,T
	V106A
	Y181C
	Y188C/L
	M230L
	P236L

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Table 3: Mutations leading to PI resistance (modified from ANRS – AC 11 Groupe Resistance, Sept. 2002, <http://hiv.net/link.php?id=138>, and De Mendoza 2002, Shafer 2002a-c, Drug Resistance Mutations Group of the International AIDS Society-USA 2001)

Pis	Relevant primary mutations*	Further mutations associated with resistance*
Indinavir	M46I/L V82A/F/S/T L84V	V32I, F53L, I54V/L, L90M
Saquinavir	G48V L84V L90M	F53L, I54V/L, V82A/F/S/T
Nelfinavir	D30N L84V N88S/D L90M	M46I/L, G48V, F53L, I54V/L, V82A/F/S/T
Ritonavir	V82A/F/S/T L84V	V32I, M46I/L, I50V, F53L, I54V/L, L90M
Amprenavir	I50V (esp. with M46I, I47V)	L10I, V32I, M46I/L, I47V, I54L/M/V, V82A/F/I/T/S, I84V, L90M
Lopinavir	≥ 6-8 of the following mutations: L10F/I/R/V, K20M/R, L24I, M46I/L, I50V, F53L, I54L/T/V, L63P, A71I/L/V/T, V82A/F/T, I84V, L90M	
Atazanavir <i>Preliminary data</i>	I50L – frequently in combination with A71V -	I84V, N88S
Tipranavir <i>Preliminary data</i>	≥ 3 of the following mutations: L33I/F/V, V82T, I84V, L90M	

* *Secondary mutations* at positions 10, 20, 36, 63, 71, 77 and 93, which are outside the active site, can increase resistance in the presence of primary mutations.

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Chapter 7: Drug Profiles

Bernd Sebastian Kamps

Christian Hoffmann

Abacavir (ABC)

The hypersensitivity reaction, though rare, complicates use of abacavir. Abacavir should be prescribed by HIV clinicians!

Abacavir is otherwise well tolerated, possibly causing less mitochondrial toxicity than other NRTIs, and possibly with a better future. Unfortunately, there is cross-resistance to many other NRTIs.

Trade name: Ziagen[®], Trizivir[®]

Formulations: Ziagen[®] : 300 mg tablets; 20 mg/ml oral solutions, 240 ml

Trizivir[®]: Tablets containing 300 mg abacavir **and** 150 mg lamivudine **and** 300 mg zidovudine

Drug class: NRTI

Manufacturer: GlaxoSmithKline

Indication: HIV infection

Oral dose: 300 mg bid. Abacavir can be taken with or without food.

Side effects: Abacavir causes a hypersensitivity syndrome (HSR) in ca. 2 to 6 % of patients. This usually occurs within the first six weeks after initiation of treatment. Pruritus and rash are common, but may also be absent. The HSR may present only with fever and slowly developing malaise. Gastrointestinal complaints (nausea, vomiting, diarrhea, abdominal pain) and fatigue are also possible, but not necessarily linked to the HSR. Elevated liver function tests, insomnia and dizziness are rare. There is probably a genetic predisposition for the HSR.

Comments/Warnings: Abacavir is contraindicated in cases with previously diagnosed abacavir hypersensitivity and after interruption of therapy, if a prior HSR cannot be ruled out retrospectively. Patients should be well advised on the HSR, but not frightened. With only mild symptoms (see below), abacavir should not be stopped too quickly, as an intercurrent infection may "simulate" the HSR. Therapy may be continued for one or two days under close observation. Rechallenge after suspected HSR is contraindicated, as a repeated allergic reaction can be fatal.

Patients should be told to consult a doctor **immediately** if at least two of the following symptoms occur:

- fever
- shortness of breath, sore throat or cough
- rash (erythema and/or pruritus)
- nausea or vomiting or diarrhea or abdominal pain
- extreme fatigue or diffuse pain or general malaise

Interactions: 0.7 g/kg ethanol (e.g. 0.5 l wine) increases the AUC of abacavir by 41 % and increases half-life by 26 %.

Internet sources:

USA: <http://hiv.net/link.php?id=53>

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Agenerase® see Amprenavir

Amprenavir (APV)

Due to the high pill burden, unboosted dosing of amprenavir is hardly acceptable today. When boosted with ritonavir, amprenavir is well suited for salvage therapy because of an interesting resistance profile. The availability of the prodrug fos-amprenavir will presumably make this drug more attractive in the future.

Trade name: Agenerase®

Formulations:

50 mg capsules

150 mg capsules

15 mg/ml oral solution, 240 ml

Drug class: Protease inhibitor

Manufacturer: GlaxoSmithKline

Indication: HIV infection with previous PI-treatment

Oral dose: 8 capsules amprenavir bid of 150 mg each (1200 mg bid)

or

4 capsules amprenavir bid of 150 mg each (600 mg bid) **plus**
100 mg ritonavir bid

or

8 capsules amprenavir qd of 150 mg each (1200 mg qd) **plus**
200 mg ritonavir qd

Dose of amprenavir solution: 1.5 ml/kg bid. Important note: Bioavailability of amprenavir oral solution is 14 % lower than the capsulated formulation; as a result Agenerase[®] capsules and oral solution are not interchangeable on a milligram-per-milligram basis. Amprenavir solution is dosed higher: 17 mg/kg tid (=1.1 ml/kg tid), with a maximum total dose of 2800 mg daily.

Dose adjustment in hepatic impairment:

Child-Pugh score 5-8: 450 mg bid; 9-12: 300 mg bid.

Side effects: Mostly gastrointestinal with nausea, vomiting, diarrhea, flatulence, tenesmus, perioral paresthesia. Occasionally headache, fatigue; rash in 5-10 % of patients, usually in the second week of treatment. A Stevens-Johnson syndrome is rare (<1 %).

In combination with ritonavir, more frequent elevations of cholesterol, triglycerides and transaminases. Lowered glucose tolerance, rarely diabetes mellitus. Lipodystrophy.

Comments/Warnings: Amprenavir is contraindicated in pregnancy and in children under 4 years; and as concurrent treatment with rifampicin, ergotamines, cisapride, bepridil, pimozide, midazolam and triazolam. Concurrent treatment with amiodarone, warfarin, lidocaine, tricyclic anti-depressants, quinidine, cyclosporine and tacrolimus should be avoided. Amprenavir is not recommended for concurrent treatment with lovastatin, simvastatin, carbamazepine, phenobarbital, phenytoin or sildenafil (Viagra®: increased incidence of hypotension, priapism!)

Use with caution in patients with a history of sulfonamide allergy.

Concurrent treatment with rifabutin: Reduce rifabutin dose by 50%.

Amprenavir should be taken at least one hour before or after antacids or didanosine. Dose adjustment (measure plasma levels!) should be considered in combination with lopinavir.

Amprenavir solution contains 50 % propylene glycol. It is therefore contraindicated in children less than 4 years old, pregnant women, patients with renal or liver failure, and for concurrent administration with disulfiram or metronidazole.

Internet sources:

USA: Capsules: <http://hiv.net/link.php?id=61>, Solution:
<http://hiv.net/link.php?id=62>, Combination with ritonavir:
<http://hiv.net/link.php?id=63>

References:

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Atazanavir (AZV)

Atazanavir is the first once-daily PI, and has an antiviral potency that should be comparable to nelfinavir. In comparison to boosted PIs, atazanavir is slightly weaker, but has a favorable lipid profile. Whether this will have an effect on lipodystrophy still needs to be shown.

First approval is expected in spring of 2003.

Trade name: Reyataz[®]

Formulations: 200 mg capsules

Drug class: Protease inhibitor (PI)

Manufacturer: Bristol-Myers Squibb

Indication: HIV infection

Oral dose: 400 mg qd, with a meal if possible.

Side effects: Relatively frequent increases in bilirubin, so far not limiting treatment. Diarrhea in ca. 30 %. In addition: nausea, vomiting, headache, abdominal pain. These complaints usually resolve within the first weeks of treatment. In contrast to other PIs: No dyslipidemia. The effect on lipodystrophy remains unknown.

Comments/Warnings: Concurrent treatment with efavirenz reduces plasma levels of atazanavir. In one study (O'Mara et al. 2002) this was compensated by additional administration of 200 mg ritonavir.

Rifabutin has no effect on the pharmacokinetics of atazanavir.

References:

1. Agarwala S, Mummaneni V, Randall D, et al. Pharmacokinetic effect of rifabutin on atazanavir with and without ritonavir in healthy subjects. Abstract 445, 9th CROI 2002, Washington, USA. <http://www.retroconference.org/2002/Abstract/13619.htm>
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Combivir®

Formulations: Tablets containing 150 mg lamivudine **and** 300 mg zidovudine.

Drug class: Nucleoside reverse transcriptase inhibitor (NRTI).

Manufacturer: GlaxoSmithKline.

Indication: HIV infection.

Oral dose: 1 tablet bid.

With reduced renal function (creatinine clearance below 50 ml/min) and anemia, Combivir® should be replaced with the individual drugs to adjust doses of lamivudine and zidovudine.

Warnings and side effects: see chapters on lamivudine and zidovudine.

Internet sources:

USA: <http://hiv.net/link.php?id=68>

Coviracil® see Emtricitabine

Crixivan® see Indinavir

d4T see Stavudine

ddC see Zalcitabine

ddI see Didanosine

Delavirdine (DLV)

Delavirdine is rarely used, due to impractical dosing and drug interactions, and it has been completely marginalized by the other two NNRTIs nevirapine and efavirenz. However, the drug has some theoretical potential: It is fairly well tolerated (no he-

patotoxicity, no CNS problems), and increases levels of indinavir and saquinavir. If more data was available, delavirdine could be an alternative to ritonavir for boosting. It has the usual NNRTI cross-resistance.

Trade name: Rescriptor[®]

Formulations:

100 mg tablets

200 mg tablets

Drug class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).

Manufacturer: Pfizer.

Indication: HIV infection.

Oral dose: 400 mg tid.

Side effects: Rash, usually occurring within the first six weeks of treatment. In uncomplicated cases, symptomatic treatment with antihistamines. If systemic effects such as fever, conjunctivitis, myalgia and arthralgia occur, delavirdine should be discontinued. Nausea, elevated transaminases.

Comments/Warnings: Delavirdine is contraindicated for concurrent treatment with rifabutin, rifampin, carbamazepine, phenytoin, alprazolam, astemizole, phenobarbital, cisapride, midazolam, terfenadine and triazolam.

There is little data on combination with nelfinavir, lopinavir and ritonavir. Amprenavir levels seem to be reduced by delavirdine.

Delavirdine interacts with numerous drugs via reduction of CYP3A-activity. It increases the AUC of sildenafil, dapsone, clarithromycin, quinidine and warfarin. Delavirdine levels are lowered by didanosine, H₂ blockers, carbamazepine, phenytoin and antacids.

Patients should know that they may also dissolve delavirdine in water: stir tablets in a glass for a few minutes and drink. Rinse the glass with a small amount of water and drink the rest.

Internet sources:

USA: <http://hiv.net/link.php?id=178>

References:

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Didanosine (ddI)

Important, well investigated and frequently used NRTI. Combination with stavudine can be problematic as there are cumulative toxicities. Even though once-daily dosing is possible, the drug must be taken on an empty stomach, and many antiretroviral drugs must be taken at intervals before or after didanosine.

Trade name: Videx[®]

Formulations:

Buffered tablets: 25 mg, 50 mg, 100 mg, 200 mg

EC capsules: 125 mg, 200 mg, 250 mg, 400 mg

2 g/100 ml pediatric powder

4 g/200 ml pediatric powder

Drug class: NRTI.

Manufacturer: Bristol-Myers Squibb.

Indication: HIV infection.

Oral dose: 400 mg qd (body weight > 60 kg) or 250 mg qd (body weight < 60 kg). Didanosine must be taken on an empty stomach, at least 2 hours after or 1 hour before meals.

Side effects: Diarrhea, nausea, headache, rash. Pancreatitis, even after longer periods on treatment! Peripheral polyneuropathy. Rarely lactic acidosis, especially in combination with stavudine.

Comments/Warnings: Acute and chronic pancreatitis are contraindications – caution in patients with alcoholism! If possible, concurrent treatment with drugs that cause pancreatitis (e.g. intravenous pentamidine) should be avoided. The following drugs should be used with caution: ethambutol, cisplatin, disulfiram, ethionamide, INH, vincristine, etc. (peripheral neuropathy).

Concurrent treatment with indinavir, zalcitabine, dapsone, ketoconazole, itraconazole, or tetracyclines should be given 2 hours before or after didanosine. Dose reduction is necessary for concurrent treatment with tenofovir!

Initially, monthly monitoring of amylase, blood count, transaminases, bilirubin. Patients should be informed about the risk of pancreatitis. Didanosine should be discontinued if there is clinical suspicion for pancreatitis, with no rechallenge.

Internet sources:

USA: <http://hiv.net/link.php?id=86>

References:

1. Conway B, Wainberg MA, Hall D, et al. Development of drug resistance in patients receiving combinations of zidovudine, didanosine and nevirapine. *AIDS* 2001, 15: 1269-74. <http://amedeo.com/lit.php?id=11426071>
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Efavirenz (EFV)

Efavirenz is a frequently used NNRTI, with uncontested antiretroviral potency. It has multiple CNS side effects, for which pathogenesis is not sufficiently understood. Drug interactions have been documented for a variety of drugs commonly prescribed to HIV patients.

Trade name: Sustiva[®], Stocrin[®]

Formulations:

50 mg capsules

100 mg capsules

200 mg capsules

600 mg capsules

Drug class: NNRTI

Manufacturer: Bristol-Myers Squibb, MSD

Indication: HIV infection

Oral dose: 600 mg daily (3 capsules qd of 200 mg each or 1 capsule qd of 600 mg), preferably before going to bed.

Side effects: Nightmares, confusion, dizziness, somnolence, abnormal thinking, impaired concentration, insomnia, depersonalization. These CNS symptoms usually resolve substantially after a few weeks. A rash (15 %) may also occur in the first weeks, but severe cases of blistering, desquamating and ulceration are rare.

Elevation of liver functions and biliary enzymes, especially γ GT; hypercholesterinemia, hypertriglyceridemia.

Comments/Warnings: Contraindicated in pregnancy!

Contraindicated for concurrent treatment with ergotamines, as-temizole, cisapride, midazolam, terfenadine und triazolam. Should not be combined with contraceptive pills.

Should not be given in combination with saquinavir or amprenavir without ritonavir boost (insufficient plasma levels of saquinavir and amprenavir).

Dose adjustments in combination with

- Lopinavir: Increase lopinavir dose to 4 capsules bid.
- Indinavir: Increase indinavir dose to 1000 mg tid.
- Rifabutin: Increase rifabutin dose to 450 to 600 mg/day.
- Methadone: Possibly increase methadone dose by 20 bis 40 %.

When switching therapy from a PI to efavirenz, overlapping therapy is recommended for one week.

Efavirenz should not be taken with fatty meals, as this reduces absorption.

Internet sources:

USA: <http://hiv.net/link.php?id=88>

References:

1. Boffito M, Rossati A, Reynolds HE, et al. Undefined duration of opiate withdrawal induced by efavirenz in drug users with hiv infection and undergoing chronic methadone treatment. *AIDS Res Hum Retroviruses* 2002, 18: 341-2.
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<http://amedeo.com/lit.php?id=10601505>

Emtricitabin (FTC)

Emtricitabine is a well tolerated NRTI, comparable to lamivudine in its resistance profile. It can be taken once a day.

Trade name: Coviracil[®]

US application for approval in September 2002

Drug class: NRTI

Manufacturer: Triangle Pharmaceuticals, now: Gilead

Indication: HIV infection

Oral dose: 200 mg qd

Side effects: Rare. Most commonly headache, nausea, gastrointestinal complaints.

References:

1. Benson C, et al. Overview of the comparative effectiveness of triple combination therapy regimens of emtricitabine (FTC) and lamivudine (3TC) in antiretroviral-naïve HIV-1 infected adults. XIV International AIDS Conference, Barcelona 2002. Abstract TuPeB4430. <http://hiv.net/link.php?id=91>
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<http://www.retroconference.org/2001/abstracts/abstracts/abstracts/321.htm>
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CROI 2001, Chicago, USA.

<http://www.retroconference.org/2001/abstracts/abstracts/abstracts/18.htm>

Enfuvirtide see T-20

Epivir[®] see Lamivudine

Fortovase[®] see Saquinavir

Fuzeon[®] see T-20

Hivid[®] see Zalcitabine

Indinavir (IDV)

Effective and well-investigated PI, the use of which is slightly limited due to skin, kidney and intestinal problems. There is multiple cross-resistance to other PIs, but the drug has good CNS penetration. Today, indinavir is generally used with ritonavir boosting, which simplifies dosing.

Trade name: Crixivan[®]

Formulations:

200 mg capsules

333 mg capsules

400 mg capsules

Drug class: Protease inhibitor (PI)

Manufacturer: Merck

Indication: HIV infection

Oral dose: In combination with ritonavir: 800 mg bid (two 400 mg capsules bid) plus 100 mg ritonavir bid (one 100 mg capsule bid)

or

400 mg bid (one 400 mg capsule bid) plus 400 mg ritonavir bid (four 100 mg capsules bid).

Without ritonavir boosting: 800 mg tid (two 400 mg capsules tid) one hour before or two hours after meals. Impaired liver function: 600 mg tid (three 200 mg capsules tid).

Side effects: Nephrolithiasis (in up to 25 %). Less frequently: nephrotoxicity with elevated serum creatinine. Diarrhea, nausea, vomiting.

A sicca syndrome occurs relatively frequently (dry skin, mouth, eyes); ingrown toenails and paronychia; rarely alopecia. Asymptomatic hyperbilirubinemia.

Lipodystrophy ("Crixbelly"), dyslipidemia, disorders of glucose metabolism.

Comments/Warnings: The concurrent use of rifampicin, as-temizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, or St. John's wort is contraindicated.

The following dose adjustments are necessary:

- Rifabutin: 1000 mg indinavir tid + 150 mg rifampicin.
- Lopinavir: 600 mg indinavir bid.
- Ketoconazole and itraconazole: 600 mg indinavir tid.
- Sildenafil: maximum 25 mg sildenafil/48h.

Unboosted, indinavir must be taken on an empty stomach. At least 1.5 l of fluid should be consumed daily to prevent nephrolithiasis. Symptoms must be explained (hematuria, flank pain). The occurrence of nephrolithiasis and skin problems correlates with plasma levels.

Didanosine decreases indinavir absorption. Combination of the two drugs is therefore generally avoided.

In combination with ritonavir, indinavir can be taken twice daily and with meals. Sufficient fluid intake is still necessary.

Internet sources:

USA: <http://hiv.net/link.php?id=102>

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Invirase[®] see Saquinavir

Kaletra[®] see Lopinavir

Lamivudine (3TC)

Well tolerated drug, but rapid development of resistance. Lamivudine is frequently used as a component of the fixed combination tablets Combivir[®] and Trizivir[®]. It is also effective against hepatitis B virus.

Trade name: Epivir[®], Combivir[®], Trizivir[®]

Formulations: Epivir[®]: 150 mg tablets; 300 mg tablets, 10 mg/ml oral solution, 240 ml

Combivir[®]: Tablets containing 150 mg lamivudine **and** 300 mg zidovudine

Trizivir[®]: Tablets containing 150 mg lamivudine **and** 300 mg zidovudine **and** 300 mg abacavir

Class: NRTI

Manufacturer: GlaxoSmithKline

Indication: HIV infection

Oral dose Epivir[®]: 300 mg qd or 150 mg bid. Dose adjustment is required with reduced creatinine clearance:

Creatinine clearance (ml/min)	Dose
30–49	150 mg qd
15–29	150 mg first dose, then 100 mg qd
5–14	150 mg first dose, then 50 mg qd
<5	50 mg first dose, then 25 mg qd

Children receive 4 mg/kg, with a maximum of 150 mg bid.

Oral dose Combivir[®]: 1 tablet bid, containing 150 mg lamivudine and 300 mg zidovudine.

Oral dose Trizivir[®]: 1 tablet bid, containing 150 mg lamivudine and 300 mg zidovudine and 300 mg abacavir.

Patients with a creatinine clearance < 50 ml/min or with impaired liver function should not receive Combivir[®] or Trizivir[®], but rather the individual formulations of zidovudine and lamivudine.

Side effects: Fatigue, nausea, vomiting, diarrhea, headache, insomnia, myalgia and arthralgia may occur, but are usually due to other drugs in the combination (see sections on zidovudine and abacavir). Peripheral polyneuropathy, pancreatitis and lactic acidosis are rare.

Comments/Warnings: Lamivudine requires dose adjustment based on renal function.

Internet sources:

USA: Epivir[®]: <http://hiv.net/link.php?id=49>, Combivir[®]: <http://hiv.net/link.php?id=50>, Trizivir[®]: <http://hiv.net/link.php?id=51>

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Lopinavir (LPV)

Kaletra[®] is a very effective and relatively well tolerated PI. Kaletra[®] is an ideal drug for salvage therapy, as it has astonishing potency in PI-experienced patients with multiple resistance mutations. It remains to be proven whether or not Kaletra[®] is superior to other boosted PIs in the initial therapy. Disadvantages include extremely high lipid levels and drug interactions.

Trade name: Kaletra[®]

Formulations: Capsules with 133.3 mg lopinavir (LPV) + 33.3 mg ritonavir (RTV); bottles of 180 capsules.

Solutions with 80 mg lopinavir + 20 mg ritonavir per ml; bottles of 160 ml.

Keep refrigerated!

Drug class: Protease inhibitor.

Manufacturer: Abbott.

Indication: HIV infection.

Oral dose: 3 capsules bid or 5 ml solution bid with meals

In combination with efavirenz or nevirapine, the dose should be increased to 4 capsules bid or 6.5 ml solution bid. Measure plasma levels!

Side effects: Mainly diarrhea, nausea, and dyslipidemia. Also: headaches, and elevated transaminases.

Comments/Warnings: Drug interactions are numerous. All drugs metabolized by the CYP3A or CYP2D6 enzyme systems are contraindicated: flecainide, propafenone, astemizole, terfenadine, ergotamines, cisapride, pimozide, midazolam, triazolam.

Rifampicin and St. John's wort reduce the efficacy of lopinavir.

Caution with: lovastatin, simvastatin (myopathy, rhabdomyolysis), carbamazepine, phenobarbital, phenytoin or sildenafil (hypotension), amiodarone, warfarin, lidocaine, tricyclic antidepressants, quinidine, cyclosporine, tacrolimus. Measure plasma levels in patients with reduced liver function tests, especially in cases with concurrent hepatitis B or C or significantly elevated transaminases.

If lopinavir is being combined with didanosine, didanosine must be taken one hour before or two hours after lopinavir. Lopinavir solution contains alcohol, therefore no co-medication with disulfiram or metronidazole. Caution with the pill (contraception not safe).

When used with rifabutin, the rifabutin dose should be reduced by 75 %, i.e. 150 mg qd every two days.

Increasing the methadone dose may be necessary.

Internet sources:

USA: <http://hiv.net/link.php?id=116>

References:

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Nelfinavir (NFV)

A relatively well tolerated and well investigated PI, but is slightly less potent than boosted PIs. A Nelfinavir-based PI regimen is less potent than NNRTI regimens. Main problems include high pill burden and frequent diarrhea. Due to its favorable resistance profile (after failure of nelfinavir treatment, other PIs may still have good efficacy), it is well suited as a first-line PI.

Trade name: Viracept®

Formulations:

250 mg tablets

50 mg/g oral powder, 144 g

Drug class: Protease inhibitor

Manufacturer: Roche

Indication: HIV infection.

Oral dose: 1250 mg bid or 750 mg tid with meals.

Side effects: Diarrhea! Meteorism, and nausea also occur. Lipodystrophy, dyslipidemia, reduced glucose tolerance.

Comments/Warnings: Contraindicated for co-medication with rifampicin, the pill, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, and St. John's wort.

In combination with rifabutin: 150 mg rifabutin qd and increase nelfinavir dose to 1000 mg tid.

Methadone: If withdrawal symptoms occur, dose may be increased.

Sildenafil: maximum 25 mg/48 h.

Nelfinavir should be taken with meals. Diarrhea can usually be controlled with loperamide (2 mg with each fluid bowel movement, up to a maximum of 16 mg/day).

Boosting with ritonavir is not advisable, as levels are not significantly changed.

Internet sources:

USA: <http://hiv.net/link.php?id=118>

References:

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Nevirapine (NVP)

Nevirapine is a frequently prescribed NNRTI. As with all NNRTIs, a single point mutation is sufficient to develop a high-level resistance. Nevirapine is very useful for simplification of successful HAART regimens. It has a good long-term tolerability with a favorable lipid profile. The main problem, besides development of resistance, is hepatotoxicity in the first months of treatment (see below).

Nevirapine is effective for prophylaxis of mother-to-child transmission.

Trade name: Viramune[®]

Formulations:

200 mg tablets

10 mg/ml suspension, 240 ml

Drug class: Non-nucleoside reverse transcriptase inhibitor (NNRTI)

Manufacturer: Boehringer-Ingelheim

Indication: HIV infection

Oral dose: 1 tablet bid. Always start with lead-in dosing! The initial lead-in dose (1 tablet/day over two weeks) reduces the frequency of rash. For resumption of treatment after treatment interruption, lead-in dosing is generally not necessary if the drug was well tolerated before. Due to its long half-life, nevirapine should be discontinued three days before other backbone drugs are administered, in order to prevent the development of resistance. Nevirapine may be taken on an empty stomach or with meals.

Side effects: Mainly hepatotoxicity, rash. Less frequently: fever, nausea, drowsiness, headache, myalgia. These side effects may occur with or without hepatotoxicity and/or rash. γ GT is frequently elevated.

To detect hepatotoxicity (occurring in 15 %; defined as an increase in transaminases to at least three times the upper limit of normal), liver function tests should be monitored biweekly for the first two months. Thereafter, monthly tests are necessary, as more than half of the hepatotoxic episodes occur after the first quarter of treatment. In cases of hepatotoxicity, treatment must be interrupted until liver function tests have returned to initial levels. Treatment is restarted with 200 mg qd. The dose may be increased to 200 mg bid only after a prolonged period of observation. If liver enzymes increase again, nevirapine should be permanently discontinued. The website of the EMEA provides detailed guidelines: <http://hiv.net/link.php?id=120>.

A rash, often pruritic and usually occurring within the first six weeks of treatment, can be treated with antihistamines if mu-

cous membranes are not involved and if transaminases are normal. Topical formulations are effective against pruritus. Nevirapine must be discontinued if a severe rash occurs; in these cases, steroids may be used (eg. prednisolone 1 mg/kg for 3-5 days). Nevirapine should also be discontinued if other systemic symptoms occur (fever, conjunctivitis, myalgia, arthralgia, malaise). If the rash occurs during the first two weeks of treatment, the dose should not be increased until the rash has resolved completely. Prophylactic treatment with steroids is not advised.

Comments/Warnings:

Cautious use in hepatic dysfunction (measure plasma levels).

Contraindicated for co-medication with rifampicin, ketoconazole, St. John's wort and the pill.

Azole derivatives: Fluconazole should be used for antimycotic treatment.

Dose adjustment in combination with

- Indinavir: increase indinavir dose to 1000 mg tid.
- Methadone: if withdrawal symptoms occur, dose may need to be increased.
- Lopinavir: possibly increase Kaletra[®] dose to 4 capsules bid (measure plasma levels!)

Nevirapine has a favorable long-term profile. In particular, lipid levels are usually favorably influenced. γ GT is almost always increased during long-term treatment. Values of up to 150 U/l can be tolerated. Nevirapine should not be given for post-exposure prophylaxis.

Internet sources:

USA: <http://hiv.net/link.php?id=121>

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<http://amedeo.com/lit.php?id=11740193>

Norvir® see Ritonavir

Rescriptor® see Delavirdine

Retrovir® see Zidovudine

Ritonavir (RTV)

Due to its gastrointestinal side effects, the therapeutic dose of ritonavir is hardly acceptable and rarely prescribed. However, ritonavir has become an important drug for boosting other protease inhibitors. In these combinations, when lower doses are used, side effects of ritonavir are tolerable. Numerous drug interactions must be considered.

Trade name: Norvir®

Formulations:

100 mg capsules

80 mg/ml oral solution, 240 ml

Drug class: Protease inhibitor

Manufacturer: Abbott

Indication: HIV infection

Oral dose: In rare cases, in which ritonavir is used as a single PI, the dose is 600 mg bid (increase dose over two weeks: 300

mg bid on day 1-2, 400 mg bid on day 3-5, 500 mg bid on day 6-13).

The optimal use of ritonavir, however, is for boosting of other PIs! Daily doses in combination with

- Saquinavir (Fortovase[®] or Invirase[®]):
100 mg ritonavir bid + 1000 mg saquinavir bid
or
400 mg ritonavir bid + 400 mg saquinavir bid
- Indinavir (Crixivan[®]):
100 mg ritonavir bid + 800 mg indinavir bid
or
400 mg ritonavir bid + 400 mg indinavir bid
- Amprenavir (Agenerase[®]):
100 mg ritonavir bid + 600 mg amprenavir bid
or
200 mg ritonavir qd + 1200 mg amprenavir qd
- Lopinavir (Kaletra[®]): Fixed combination, see lopinavir.

Side effects: Very frequent with therapeutic doses: nausea, vomiting, diarrhea, headache, perioral paresthesia and electric sensations on arms and legs. Elevated transaminases and γ GT, often significant dyslipidemia, reduced glucose tolerance and, rarely, diabetes mellitus. Lipodystrophy with long-term treatment.

Comments/Warnings: Even the low boosting doses used in combination with other PIs have multiple drug interactions! The following are contraindicated: rifampicin, amiodarone, astemizole, bepridil, terfenadine, encainide, flecainide, cisapride, triazolam, ergotamine, simvastatin, lovastatin, quinidine, and St. John's wort. Sildenafil should be avoided!

Caution should be taken and plasma levels measured for both ritonavir and (if possible) the following co-medications: Methadone, immunosuppressants (cyclosporine, tacrolimus), macro-

lide antibiotics (erythromycin, clarithromycin), steroids, calcium antagonists, tricyclic antidepressants, other antidepressants (fluoxetine, paroxetine, sertraline), neuroleptics (haloperidol, risperidone, thioridazine), antimycotic drugs (ketoconazole, itraconazole), carbamazepine, tolbutamide, rifabutin, theophylline, and warfarin.

Internet sources:

USA: <http://hiv.net/link.php?id=31>

References:

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Saquinavir (SQV)

One of the first PIs, and the only one with two available formulations. Relatively "benign" (well tolerated except for gastrointestinal problems, no serious short-term problems). Intolerable pill burden if unboosted. Due to low bioavailability, the formulation was improved from Invirase[®] to Fortovase[®], which is unfortunately less well tolerated. According to recent data, Invirase[®], which had almost been abandoned, is just as effective when boosted with ritonavir. Strangely enough, Invirase[®] is significantly more expensive. Cross-resistance with other PIs is frequent.

Trade name: Fortovase[®], Invirase[®]

Formulations:

200 mg capsules (Invirase[®])

200 mg soft gel capsules (Fortovase[®])

Drug class: Protease inhibitor

Manufacturer: Hoffmann-La Roche

Indication: HIV infection

Oral dose: Treatment without boosting (only in exceptions): 1200 mg tid (6 capsules tid). Combination with ritonavir is generally preferred:

Fortovase[®] or Invirase[®]: 1000 mg bid plus 100 mg ritonavir bid is optimal. An alternative is 400 mg ritonavir bid plus 400 mg Fortovase[®] or Invirase[®].

Side effects: Mainly gastrointestinal: diarrhea, nausea, abdominal discomfort, meteorism. Rarely elevation of transaminases or γ GT, headache. As with other PIs, lipodystrophy, dyslipidemia and reduced glucose tolerance may occur with long-term treatment.

Comments/Warnings: Contraindicated for concurrent treatment with rifampicin, astemizole, terfenadine, cisapride, triazolam, ergotamine, simvastatin, lovastatin, and St. John's wort.

If saquinavir is not combined with other protease inhibitors it must be taken with meals.

Internet sources:

USA: <http://hiv.net/link.php?id=132>

References:

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Stavudine (d4T)

Stavudine is a thymidine analog like zidovudine. Subjective tolerability is good; the drug was long considered at least equivalent to zidovudine. Newer guidelines are more cautious, due to neuropathy and data on mitochondrial toxicity (lipoatrophy, lactic acidosis), particularly in combination with didanosine. New 75 mg and 100 mg capsules will be available shortly, allowing once-daily dosing.

Trade name: Zerit[®]

Formulations:

Capsules: 15 mg, 20 mg, 30 mg, 40 mg

1 mg/ml oral solution, 200 ml

Extended-Release Capsules, 37.5 mg, 50 mg, 75 mg, and 100 mg, available later in 2003

Drug class: NRTI

Manufacturer: Bristol-Myers Squibb

Indication: HIV infection

Oral dose: 40 mg bid (body weight > 60 kg), or 30 mg bid (body weight < 60 kg). In renal failure:

Weight	Creatinine clearance 26-50 ml/min	Creatinine clearance below 26 ml/min (incl. dialysis patients)*
<60 kg	15 mg bid	15 mg qd
>60 kg	20 mg bid	20 mg qd

* Hemodialysis: patients should take Zerit after dialysis and at the same time on non-dialysis days.

Side effects: Peripheral neuropathy, especially in combination with didanosine (up to 24 %). In many studies, stavudine has been linked to lipatrophy more than other NRTIs. However, the following are less frequent than with zidovudine: diarrhea, nausea, vomiting, headache. Very rare, but potentially fatal: lactic acidosis which occurs mostly in combination with didanosine (especially in pregnancy!). Further side effects: hepatic steatosis, pancreatitis.

Comments/Warnings: Stavudine should not be combined with zidovudine due to antagonistic effects.

If possible, no concurrent treatment with other neurotoxic drugs (zalcitabine, ethambutol, cisplatin, INH, vincristine, etc.)

Stavudine can be taken on an empty stomach or with a light meal. If symptoms of peripheral neuropathy occur, treatment with stavudine should be discontinued.

Internet sources:

USA: <http://hiv.net/link.php?id=80>

References:

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5. Yogev R, Lee S, Wiznia A, et al. Stavudine, nevirapine and zidovudine in stable antiretroviral therapy- experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J* 2002, 21: 119-125.
<http://amedeo.com/lit.php?id=11840078>

Stocrin[®] see Efavirenz

Sustiva[®] see Efavirenz

T-20 (Enfuvirtide)

T-20 is the prototype of a new drug class – the entry inhibitors. It is well tolerated, but can only be administered as an injection. It will be important for salvage therapy in the future.

Trade name: Fuzeon[®]

Formulations: Vials, 90 mg; supplied as 30-day kit with tools required for self-injection. The powder is reconstituted with sterile water prior to subcutaneous injection.

Drug class: Fusion inhibitor (or entry inhibitor)

Manufacturer: Hoffmann-La Roche

Indication: T-20 in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

Dose: 90 mg subcutaneously bid. In pediatric patients six years through 16 years of age, a dose of 2 mg per kg of body weight (maximum 90 mg) administered twice-daily, provided plasma concentrations similar to those obtained in adult patients receiving 90 mg, twice-daily.

Side effects: Generally well tolerated. Local injection site reactions are the most frequent adverse events associated with the use of T-20. In Phase III clinical studies, 98 percent of patients had at least one local reaction at the injection site. Manifestations of injection site reactions may include pain and discomfort, induration, erythema, nodules and cysts, prurities, and ecchymosis (change injection site).

Hypersensitivity reactions have been associated with T-20 (<1 %) and have recurred on rechallenge. Symptoms of an allergic reaction may include rash, fever, nausea and vomiting, chills, rigors, hypotension, and elevated serum transaminases.

References:

1. Clotet B, Lazzarin A, Cooper D, et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience resistance to each of the three classes of approved antiretrovirals in Europe and Australia. Abstract LbOr19A, XIV International AIDS Conference 2002, Barcelona, Spain.
2. Henry K, Lalezari J, O'Hearn M, et al. Enfuvirtide (T-20) in combination with an optimized background (OB) regimen vs. OB alone in patients with prior experience resistance to each of the three classes of approved antiretrovirals in North America and Brazil. Abstract LbOr19B, XIV International AIDS Conference 2002, Barcelona, Spain.
3. Kilby JM, Hopkins S, Venetta TM, et al. Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. *Nat Med.* 1998, 4:1302-1307.
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<http://63.126.3.84/2002/Abstract/13592.htm>
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Engl J Med 2003; published at www.nejm.org on Mar 13, 2003. Full-text article: <http://hiv.net/link.php?id=215>

Tenofovir (TDF)

Tenofovir DF is the prodrug of the acyclic nucleotide analog tenofovir, and has good oral bioavailability. It also has efficacy against hepatitis B virus. Tenofovir, at least according to current data, has good tolerability.

Trade name: Viread[®]

Formulations: 300 mg tablets

Drug class: Nucleotide reverse transcriptase inhibitor

Manufacturer: Gilead

Indication: Previously treated HIV infection (approval for initial therapy is expected in 2003)

Oral dose: 300 mg qd, to be taken with a meal.

Side effects: Generally well tolerated. In several studies, side effects were comparable to those reported in placebos. Rarely: elevation of liver enzymes; possibly leucopenia.

It is not currently known, whether long-term treatment with tenofovir can lead to bone density changes. Animal studies showed changes in bone density at doses 30 times higher than the therapeutic dose. In contrast to its predecessor, adefovir, there has been no indication of nephrotoxicity – however, there is no long-term data available yet.

Comments/Warnings: Tenofovir should not be prescribed to patients with a creatinine clearance of less than 60 ml/min. In cases of mild renal dysfunction, retention parameters should be monitored monthly. Concurrent treatment of tenofovir and other drugs that are eliminated via active tubular secretion can lead to increased serum concentrations of both drugs: cidofovir, aciclovir, valaciclovir, ganciclovir, valganciclovir.

Use with caution in combination with didanosine: co-medication with tenofovir increases the C_{max} and AUC of di-

danosine by 28 % and 44 %, respectively. Even though the data published so far does not show an increased incidence in the side effects typical of didanosine, the dose of didanosine should be reduced to 250 mg. Tenofovir should be taken two hours before or one hour after didanosine.

Controlled studies on the use of tenofovir in pregnancy are yet to come. In monkey studies, tenofovir was effective in the prophylaxis of SIV transmission, but also resulted in growth disorders.

Internet sources:

USA: <http://hiv.net/link.php?id=134>

References:

1. Barditch-Crovo P, Deeks SG, Collier A, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in HIV-infected adults. *Antimicrob Agents Chemother* 2001, 45:2733-9. <http://amedeo.com/lit.php?id=11557462>
2. Birkus G, Hitchcock JM, Cihlaret T. Mitochondrial toxicity of nrtis: in vitro assessment and comparison with tenofovir. Abstract 708, 9th CROI 2002, Seattle, USA. <http://63.126.3.84/2002/Abstract/13560.htm>
3. Bochet M, Tubiana R, Benhamou Y, et al. Tenofovir disoproxil fumarate suppresses lamivudine resistant HBV-replication in patients coinfectd with HIV/HBV. Abstract 675, 9th CROI 2002, Seattle, USA. <http://www.retroconference.org/2002/Abstract/13910.htm>
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therapy: 48-week interim results. Abstract LB17, XIV International AIDS Conference 2002, Barcelona, Spain.

Tipranavir

Tipranavir is the first non-peptide PI and shows good efficacy against PI-resistant viruses. It has low oral bioavailability and therefore requires boosting with ritonavir.

Tipranavir is still under clinical investigation.

Drug class: Non-peptide protease inhibitor (NPPI)

Manufacturer: Boehringer-Ingelheim

Indication: HIV infection

Oral dose: Tipranavir is being tested in Phase III studies at a dose of 500 mg bid plus 200 mg ritonavir bid.

Side effects: Diarrhea, vomiting, headache, abdominal pain. Rarely: dizziness, fatigue, elevated transaminases.

Comments/Warnings: Co-medication with rifampicin and delavirdine is contraindicated. Antacids reduce tipranavir levels by 30 %.

References:

1. Larder BA, Hertogs K, Bloor S, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. AIDS 2000, 14:1943-8. <http://amedeo.com/lit.php?id=10997398>
2. McCallister S, Sabo J, Galitz L, Mayers D. An open-label steady state investigation of the pharmacokinetics of tipranavir and ritonavir and their effects on cytochrome P-450 (3A4) activity in normal healthy volunteers (BI 1182.5). Abstract 434, 9th CROI 2002, Seattle, USA. <http://63.126.3.84/2002/Abstract/13434.htm>
3. Rusconi S, La Seta Catamancio S, Citterio P, et al. Susceptibility to PNU-140690 (tipranavir) of HIV type 1 isolates derived from patients with multidrug resistance to other protease inhibitors. Antimicrob Agents Chemotherapy 2000, 44:1328-32. <http://amedeo.com/lit.php?id=10770770>
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antiretroviral-naïve HIV-1-infected patients. Abstract 673, 7th CROI, San Francisco, USA. <http://www.retroconference.org/2000/abstracts/673.htm>

Trizivir®

This combination has led to a significant reduction in the pill burden. It is the simplest triple combination currently available. See also the individual drugs zidovudine, lamivudine and abacavir.

Formulations:

Tablets containing 150 mg lamivudine **and** 300 mg zidovudine **and** 300 mg abacavir.

Drug class: Nucleoside reverse transcriptase inhibitors (NRTI)

Manufacturer: GlaxoSmithKline

Indication: HIV infection

Oral dose: 1 tablet bid. In cases of impaired renal function (creatinine clearance less than 50 ml/min), the individual drugs should be given separately to allow the doses of lamivudine and zidovudine to be adjusted.

Side effects: Mostly gastrointestinal, see the individual drugs. Hypersensitivity reaction with abacavir (see under abacavir!). There are possible additive effects with regard to mitochondrial toxicity.

Comments/Warnings: Watch closely for hypersensitivity reactions (see abacavir). See individual drugs.

Internet sources:

USA: <http://hiv.net/link.php?id=51>

References:

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2. Opravil M, Hirschel B, Lazzarin A, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in HIV infection. *J Infect Dis* 2002, 185: 1251-60. <http://amedeo.com/lit.php?id=12001042>
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4. Vibhagool A, Cahn P, Schechter M, et al. Abacavir/Combivir (ABC/COM) is comparable to Indinavir/Combivir in HIV-1-infected antiretroviral therapy naïve adults: preliminary results of a 48-week open label study (CNA3014). Abstract 63, 1st IAS Conference on HIV Pathogenesis and Treatment 2001, Buenos Aires, Argentina.

Videx® see Didanosine

Viracept® see Nelfinavir

Viramune® see Nevirapine

Viread® see Tenofovir

Zerit® see Stavudine

Ziagen® see Abacavir

Zalcitabine (ddC)

One of the first antiretroviral drugs. It is now used very rarely due to complicated dosing, risk of polyneuropathy and cross-resistance with didanosine. It is possibly less potent than didanosine and stavudine.

Trade name: Hivid[®]

Formulations:

0.375 mg tablets

0.75 mg tablets

Drug class: NRTI

Manufacturer: Hoffmann-La Roche

Indication: HIV infection

Oral dose: 0.75 mg tid. Dose adjustment for renal failure: Creatinine clearance of 40 to 10 ml/min: 0.75 mg bid, CrCl < 10 ml/min: 0.75 mg qd.

Side effects: Peripheral neuropathy (up to 30 %), stomatitis with oral ulcers (up to 4 %), pancreatitis (<1 %). Rarely rash, lactic acidosis, hepatic steatosis.

Comments/Warnings: Zalcitabine is contraindicated in patients with pre-existing polyneuropathy. Use with caution with history of pancreatitis.

Zalcitabine should not be administered with neurotoxic drugs, e.g. ethambutol, cisplatin, disulfiram, ethionamide, INH, vincristine. Combination of didanosine and stavudine is not recommended, as there is little available data and risk of cross-resistance. Combination with zidovudine is best.

Internet sources:

USA: <http://hiv.net/link.php?id=84>

References:

1. Adkins JC, Peters DH, Faulds D. Zalcitabine. An update of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in the management of HIV infection. *Drugs* 1997; 53: 1054-80. <http://amedeo.com/lit.php?id=9179531>

Zidovudine (AZT)

The oldest and best investigated HIV drug. Due to gastrointestinal and myelotoxic side effects, the drug was out of fashion for a while. However, it remains an important component of many HAART regimens even today, particularly as it has good CNS penetration and relatively low mitochondrial toxicity (good long-term tolerability!).

Trade name: Retrovir[®], Combivir[®], Trizivir[®]

Formulations: Retrovir[®]: 100 mg capsules, 250 mg capsules, 300 mg tablets

10 mg/ml syrup, 240 ml

20 ml intravenous vials, 10 mg/ml

Combivir[®]: Tablets containing 300 mg zidovudine **and** 150 mg lamivudine

Trizivir[®]: Tablets containing 300 mg zidovudine **and** 150 mg lamivudine **and** 300 mg abacavir

Manufacturer: GlaxoSmithKline

Indication: HIV infection. Prevention of maternal-fetal HIV transmission.

Dose: 250 mg bid or 200 mg tid. In Combivir[®] and Trizivir[®] 300 mg bid.

Creatinine clearance below 20 ml/min: 300 bis 400 mg daily.

Hemodialysis: 300 mg daily. Hepatic failure: 100 mg tid.

Side effects: Nausea, vomiting, abdominal discomfort, headache, myalgia, dizziness. Macrocytic anemia (MCV almost always elevated), rarely neutropenia. Elevations in LDH, CPK and transaminases may occur. Episodes of lactic acidosis are rare.

Comments/Warnings: Do not combine with stavudine! There is increased myelotoxicity with concurrent use of other myelosuppressive drugs, especially ganciclovir, but also cotrimoxazole, dapsone, etoposide, pyrimethamine, interferon,

daunorubicin, vinblastine, vincristine, sulfadiazine, amphotericin B and ribavirin.

Ribavirin antagonizes the antiviral activity of zidovudine in vitro. Concurrent use of zidovudine and ribavirin should therefore be avoided.

Initially monthly monitoring of blood count, transaminases, CPK and bilirubin. The gastrointestinal complaints can be treated symptomatically and usually subside after a few weeks. Anemia can develop even after months.

Zidovudine should always be a component of transmission prophylaxis!

Internet sources:

USA: Retrovir[®] tablets: <http://hiv.net/link.php?id=66>

Retrovir[®] IV infusion: <http://hiv.net/link.php?id=67>

Combivir[®]: <http://hiv.net/link.php?id=68>

Trizivir[®]: <http://hiv.net/link.php?id=69>

References:

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